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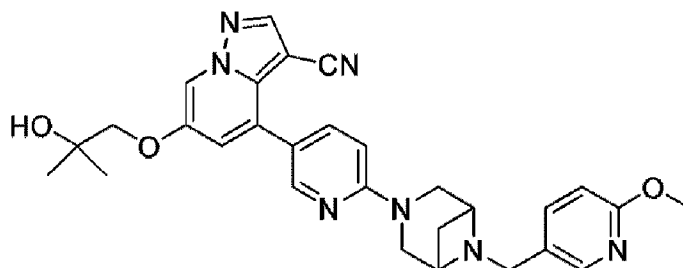
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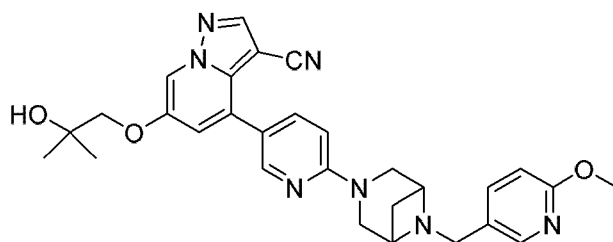
(57) Abrégé/Abstract:

The present invention relates to crystalline forms of 6-(2-hydroxy-2-methylpropoxy)-4-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula II), and pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising the compounds, processes for making the compounds, and the use of these compounds. The crystalline forms and pharmaceutically acceptable salts thereof are useful in the treatment and prevention of diseases which can be treated with a RET kinase inhibitor, including RET-associated diseases and disorders.

(see formula II)

ABSTRACT

The present invention relates to crystalline forms of 6-(2-hydroxy-2-methylpropoxy)-4-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula II), and pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising the compounds, processes for making the compounds, and the use of these compounds. The crystalline forms and pharmaceutically acceptable salts thereof are useful in the treatment and prevention of diseases which can be treated with a RET kinase inhibitor, including RET-associated diseases and disorders.



(II)

DEMANDE OU BREVET VOLUMINEUX

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CRYSTALLINE FORMS

[0001]

BACKGROUND

[0002] RET is a single-pass transmembrane receptor belonging to the tyrosine kinase superfamily that is required for normal development, maturation, and maintenance of several tissues and cell types (Mulligan, L. M., *Nature Reviews Cancer* (2014) 14:173-186). The extracellular portion of the RET kinase contains four calcium-dependent cadherin-like repeats involved in ligand binding and a juxtamembrane cysteine-rich region necessary for the correct folding of the RET extracellular domain, while the cytoplasmic portion of the receptor includes two tyrosine kinase subdomains.

[0003] RET signaling is mediated by the binding of a group of soluble proteins of the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), which also includes neurturin (NTRN), artemin (ARTN), and persephin (PSPN) (Arighi *et al.*, *Cytokine Growth Factor Rev.* (2005) 16:441-67). Unlike other receptor tyrosine kinases, RET does not directly bind to GFLs and requires an additional co-receptor: that is, one of four GDNF family receptor- α (GFR α) family members, which are tethered to the cell surface by a glycosylphosphatidylinositol linkage. GFLs and GFR α family members form binary complexes that in turn bind to RET and recruit it into cholesterol-rich membrane subdomains, which are known as lipid rafts, where RET signaling occurs.

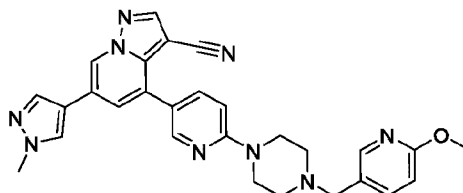
[0004] Upon binding of the ligand-co-receptor complex, RET dimerization and autophosphorylation on intracellular tyrosine residues recruits adaptor and signaling proteins to stimulate multiple downstream pathways. Adaptor protein binding to these docking sites leads to activation of Ras-MAPK and PI3K-Akt/mTOR signaling pathways or to recruitment of the CBL family of ubiquitin ligases that functions in RET downregulation of the RET-mediated functions.

[0005] Aberrant RET expression and/or activity have been demonstrated in different cancers and in gastrointestinal disorders such as irritable bowel syndrome (IBS).

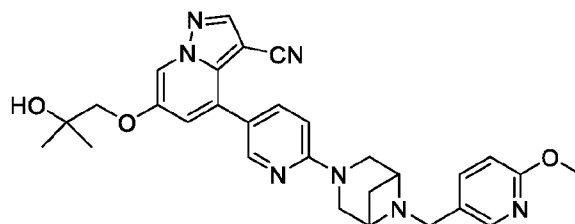
SUMMARY

[0006] Compounds of Formula I-IV, 4-(6-(4-((6-methoxypyridin-3-yl)methyl)piperazin-1-yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula I); 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula II); 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-(6-methoxynicotinoyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula III); and 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula IV) are inhibitors of RET kinase, and are useful for treating diseases such as proliferative diseases, including cancers.

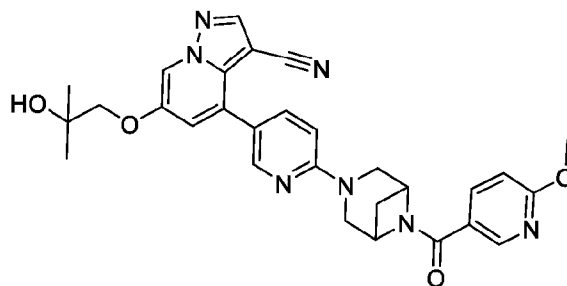
[0007] Accordingly, provided herein is a compound of Formula I-IV:

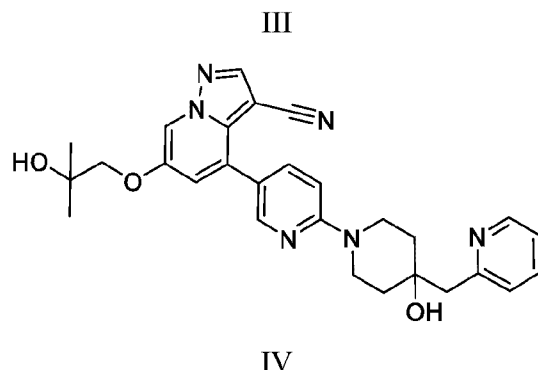


I



II





and pharmaceutically acceptable salts, amorphous, and polymorph forms thereof.

[0008] Also provided herein is a crystalline form of a compound of Formula I, wherein the crystalline form is Form A, and is characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 4.4 ± 0.2 , 14.6 ± 0.2 , and 18.3 ± 0.2 .

[0009] Also provided herein is a crystalline form of a compound of Formula II, wherein the crystalline form is Form 1, and is characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 16.5 ± 0.2 , 18.9 ± 0.2 , and 26.0 ± 0.2 .

[0010] Also provided herein is a crystalline form of a compound of Formula III, wherein the crystalline form is Form A, and is characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 17.3 ± 0.2 , 19.2 ± 0.2 , and 23.9 ± 0.2 .

[0011] Also provided herein is a crystalline form of a compound of Formula IV, wherein the crystalline form is Form A, and is characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 8.3 ± 0.2 , 16.3 ± 0.2 , and 21.9 ± 0.2 .

[0012] Also provided herein is a solid oral pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula I-IV, including pharmaceutically acceptable salts, amorphous, and polymorph forms thereof.

[0013] Also provided herein is a liquid pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula I-IV, including pharmaceutically acceptable salts, amorphous, and polymorph forms thereof.

[0014] Also provided herein is a method for treating cancer in a subject in need thereof, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form

thereof.

[0015] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition thereof as defined herein.

[0016] Also provided herein is a method of treating a RET-associated disease or disorder in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition thereof as defined herein.

[0017] Also provided herein is a method of treating cancer and/or inhibiting metastasis associated with a particular cancer in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for a pharmaceutical composition thereof as defined herein.

[0018] Also provided herein is a method for treating cancer and/or inhibiting metastasis associated with a particular cancer in a subject in need thereof, the method comprising (a) determining if the cancer is associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same; and (b) if the cancer is determined to be associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[0019] Also provided herein is a method of treating a RET-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having a RET-associated cancer a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition

comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[0020] Also provided herein is a method of treating a RET-associated cancer in a subject, the method comprising: determining if the cancer in the subject is a RET-associated cancer; and administering to a subject determined to have a RET-associated cancer a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[0021] Also provided herein is a method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, to a subject having a clinical record that indicates that the subject has dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same.

[0022] Also provided herein is a method of selecting a treatment for a subject, the method comprising selecting a treatment comprising administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, for a subject identified or diagnosed as having a RET-associated cancer.

[0023] Also provided herein is a method of selecting a treatment for a subject having a cancer, the method comprising: determining if the cancer in the subject is a RET-associated cancer; and selecting a treatment including administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, for a subject determined to have a RET-

associated cancer.

[0024] Also provided herein is a method of selecting a subject for treatment including administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, the method comprising: identifying a subject having a RET-associated cancer; and selecting the subject for treatment including administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[0025] Also provided herein is a method of selecting a subject having cancer for treatment including administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, the method comprising: determining if the cancer in the subject is a RET-associated cancer; and selecting a subject determined to have a RET-associated cancer for treatment including administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[0026] Also provided herein is the use of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, for the manufacture of a medicament for treating a RET-associated cancer in a subject.

[0027] Also provided herein is a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form

thereof, for use in treating a subject identified or diagnosed as having a RET-associated cancer.

[0028] Also provided herein is a method for inhibiting RET kinase activity in a mammalian cell, the method comprising contacting the mammalian cell with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[0029] Also provided herein is a method of treating irritable bowel syndrome in a subject, the method comprising administering to a subject identified or diagnosed as having irritable bowel syndrome a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, to the subject.

[0030] Also provided herein is a method for reducing pain associated with irritable bowel syndrome in a subject in need thereof, the method comprising administering to a subject identified or diagnosed as having irritable bowel syndrome a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, to the subject.

[0031] Also provided is a method of providing supportive care to a cancer patient, including preventing or minimizing gastrointestinal disorders, such as diarrhea, associated with treatment, including chemotherapeutic treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for a pharmaceutical composition thereof as defined herein.

[0032] Also provided herein is a method for inhibiting metastasis (e.g., brain metastasis) of a cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form

thereof. In some embodiments, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, is used in combination with another chemotherapeutic agent.

[0033] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises: (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor of step (a); and (c) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor of step (a); or (d) administering additional doses of the first RET inhibitor of step (a) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor of step (a).

[0034] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises: (a) administering one or more doses of a first RET inhibitor, to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor of step (a); (c) administering a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor of step (a); or (d) administering additional doses of the first RET inhibitor of step (a) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor of step (a);

wherein the mutation is a substitution at amino acid position 804, *e.g.*, V804M, V804L, or V804E.

[0035] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor that was previously administered to the subject; and (b) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor that was previously administered to the subject; or (c) administering additional doses of the first RET inhibitor to the subject if the subject has cancer cell that does not have a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor previously administered to the subject.

[0036] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor previously administered to the subject; and (b) administering a second RET inhibitor to the subject as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor that was previously administered to the subject; or (c) administering additional doses of the first RET inhibitor that was previously administered to the subject if the subject has cancer cell that does not have a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor that was previously administered to the subject.

[0037] Also provided herein is a method of treating a subject having a cancer, wherein the

method comprises: (a) administering one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or the pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, of step (a); and (c) administering a second RET inhibitor or a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with another anticancer agent to a subject having a cancer cell that has one or more RET inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or the pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, of step (a); or (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or the pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, of step (a) to a subject having a cancer cell that does not have a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or the pharmaceutical composition comprising a compound of Formula I-IV, for example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, of step (a).

[0038] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, has one or more RET inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, that was previously administered to the subject; (b) administering a second RET inhibitor or a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with another anticancer agent to a subject having a cancer cell that has one or more RET inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, that was previously administered to the subject; or (c) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, previously administered to a subject having a cancer cell that does not have a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, that was previously administered to the subject.

[0039] Also provided herein is a pharmaceutical combination for treating cancer (e.g., a RET-associated cancer, such as a RET-associated cancer having one or more RET inhibitor resistance mutations) in a patient in need thereof, which comprises (a) a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier, wherein the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and the additional therapeutic are formulated as separate compositions or dosages for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and of the additional therapeutic agent are

together effective in treating the cancer. Also provided herein is a pharmaceutical composition comprising such a combination. Also provided herein is the use of such a combination for the preparation of a medicament for the treatment of cancer. Also provided herein is a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer a patient in need thereof.

[0040] Also provided herein is a method for reversing or preventing acquired resistance to an anticancer drug, comprising administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, to a patient at risk for developing or having acquired resistance to an anticancer drug. In some embodiments, the patient is administered a dose of the anticancer drug (e.g., at substantially the same time as a dose of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered to the patient).

[0041] Also provided herein is a method of delaying and/or preventing development of cancer resistant to an anticancer drug in an individual, comprising administering to the individual an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, before, during, or after administration of an effective amount of the anticancer drug.

[0042] Also provided herein is a method of treating an individual with cancer who has an increased likelihood of developing resistance to an anticancer drug, comprising administering to the individual (a) an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, before, during, or after administration of (b) an effective amount of the anticancer drug.

[0043] Also provided are methods of treating an individual with a RET-associated cancer that has one or more RET inhibitor resistance mutations that increase resistance of the cancer to a first RET inhibitor (e.g., one or more amino acid substitutions in the kinase domain (e.g., amino acid positions 700 to 1012 in a wildtype RET protein), a gatekeeper amino acid (e.g., amino acid position 804 in a wildtype RET protein), the P-loop (e.g., amino acid positions 730-737 in a

wildtype RET protein), the X-DFG residue (e.g., amino acid position 891 in a wildtype RET protein), ATP cleft solvent front amino acids (e.g., amino acid positions 806-811 in a wildtype RET protein), the activation loop (e.g., amino acid positions 891-916 in a wildtype RET protein), the C-helix and loop preceding the C-helix (e.g., amino acid positions 768-788 in a wildtype RET protein), and/or the ATP binding site (e.g., amino acid positions 730-733, 738, 756, 758, 804, 805, 807, 811, 881, and 892 in a wildtype RET protein) (e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D, and/or one or more RET inhibitor resistance mutations listed in Tables 3 and 4), that include administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, before, during, or after administration of another anticancer drug (e.g., a second RET kinase inhibitor). See also J. Kooistra, G. K. Kanev, O. P. J. Van Linden, R. Leurs, I. J. P. De Esch, and C. De Graaf, "KLIFS: A structural kinase-ligand interaction database," *Nucleic Acids Res.*, vol. 44, no. D1, pp. D365-D371, 2016; and O. P. J. Van Linden, A. J. Kooistra, R. Leurs, I. J. P. De Esch, and C. De Graaf, "KLIFS: A knowledge-based structural database to navigate kinase-ligand interaction space," *J. Med. Chem.*, vol. 57, no. 2, pp. 249-277, 2014.

In some embodiments, a wildtype RET protein is the exemplary wildtype RET protein described herein.

[0044] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting.

[0045] Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

[0046] **Figs. 1A-1E** are plots of solubility of the compound of Formula I (freebase) in different solvent systems. **Fig. 1A** is a plot of solubility in DCM/EtOH. **Fig. 1B** is a plot of solubility in DMSO/EtOH. **Fig. 1C** is a plot of solubility in DMSO/H₂O. **Fig. 1D** is a plot of solubility in THF/EtOH. **Fig. 1E** is a plot of solubility in THF/H₂O.

[0047] **Figs. 2A-2G** are scans of the freebase of the compound of Formula I. **Fig. 2A** is an X-ray powder diffraction scan of the Form A of the compound of Formula I (freebase). **Fig. 2B** is an overlay of X-ray powder diffraction scans of the freebase from different lots before and after DVS analysis. **Fig. 2C** is a differential calorimetry scan of the freebase. **Fig. 2D** is an isothermic (25°C) dynamic vapor sorption scan of the freebase. **Fig. 2E** is a thermogravimetric analysis scan of the freebase. **Fig. 2F** is a FTIR spectrum of the freebase. **Fig. 2G** is a ¹H NMR spectrum of the freebase in DMSO-*d*₆.

[0048] **Fig. 3** is a differential scanning calorimetry scan of the maleic acid salt of the compound of Formula I identified in the initial salt screen.

[0049] **Fig. 4** is a differential scanning calorimetry scan of the acetic acid salt of the compound of Formula I identified in the initial salt screen.

[0050] **Fig. 5** is a differential scanning calorimetry scan of the D-malic acid salt of the compound of Formula I identified in the initial salt screen.

[0051] **Fig. 6** is a differential scanning calorimetry scan of the benzoic acid salt of the compound of Formula I identified in the initial salt screen.

[0052] **Fig. 7** is a differential scanning calorimetry scan of the L-tartaric acid salt of the compound of Formula I identified in the initial salt screen.

[0053] **Fig. 8** is a differential scanning calorimetry scan of the citric acid salt of the compound of Formula I identified in the initial salt screen.

[0054] **Fig. 9** is a differential scanning calorimetry scan of the propionic acid salt of the compound of Formula I identified in the initial salt screen.

[0055] **Fig. 10** is a differential scanning calorimetry scan of the D-tartaric acid salt of the compound of Formula I identified in the initial salt screen.

[0056] **Fig. 11** is a differential scanning calorimetry scan of the L-malic acid salt of the compound of Formula I identified in the initial salt screen.

[0057] **Fig. 12** is a differential scanning calorimetry scan of the sulfuric acid salt of the compound of Formula I identified in the initial salt screen.

[0058] **Fig. 13** is a differential scanning calorimetry scan of the hydrochloric acid salt of the compound of Formula I prepared on approximately 0.2g scale.

[0059] **Fig. 14** is a differential scanning calorimetry scan of the hydrobromic acid salt of the compound of Formula I prepared on approximately 0.2g scale.

[0060] **Fig. 15** are differential scanning calorimetry scans of the hydrochloric acid salt of the compound of Formula I prepared during the optimization process. **Fig. 15A** is the differential scanning calorimetry scan of the hydrochloric acid salt (prepared using DMA as the solvent). **Fig. 15B** is the differential scanning calorimetry scan of the hydrochloric acid salt (prepared using a mixture of DCM/EtOH) as the solvent.

[0061] **Figs. 16A-16F** are scans of the hydrochloric acid salt of the compound of Formula I prepared on 2 gram scale. **Fig. 16A** is a differential scanning calorimetry scan of the hydrochloric acid salt (prepared using DMA as the solvent). **Fig. 16B** is a isothermic (25°C) dynamic vapor sorption scan of the hydrochloric acid salt (prepared using DMA as the solvent). **Fig. 16C** is a thermogravimetric analysis scan of the hydrochloric acid salt (prepared using DMA as the solvent). **Fig. 16D** is an overlay of a differential scanning calorimetry scan and a thermogravimetric analysis scan of the hydrochloric acid salt (prepared using a mixture of DCM/EtOH as the solvent). **Fig. 16E** is an overlay of X-ray powder diffraction scans of the hydrochloric acid salt prepared using DMA or a mixture of DCM/EtOH as the solvent on different scales before and after DVS. **Fig. 16F** is a ^1H NMR spectrum of the hydrochloric acid salt in $\text{DMSO-}d^6$.

[0062] **Figs. 17A-17C** are scans of the hydrobromic acid salt of the compound of Formula I prepared on 2 gram scale. **Fig. 17A** is an overlay of a differential scanning calorimetry scan and a thermogravimetric analysis scan of the hydrobromic acid salt. **Fig. 17B** is an X-ray powder diffraction scan of the hydrobromic acid salt. **Fig. 17C** is a FTIR spectrum of the hydrobromic acid salt. **Fig. 17D** is a ^1H NMR spectrum of the hydrobromic acid salt in $\text{DMSO-}d^6$.

[0063] **Figs. 18A-18H** are scans of the L- and D-malic acid salts of the compound of Formula I. **Fig. 18A** is an overlay of a differential scanning calorimetry scan and a thermogravimetric analysis scan of the L-malic acid salt. **Fig. 18B** is an overlay of a differential scanning calorimetry scan and a thermogravimetric analysis scan of the D-malic acid salt. **Fig. 18C** is an isothermic (25°C) dynamic vapor sorption scan of the L-malic salt. **Fig. 18D** is an isothermic (25°C) dynamic

vapor sorption scan of the D-malic acid salt. **Fig. 18E** is an overlay of X-ray powder diffraction scans of the L- and D-malic acid salts. **Fig. 18F** is an overlay of FTIR spectra of the L- and D-malic acid salts. **Fig. 18G** is a ^1H NMR spectrum of the malic acid salt in $\text{DMSO}-d^6$. **Fig. 18H** is a ^1H NMR spectrum of the malic acid salt in $\text{DMSO}-d^6$. **Figs. 18I-M** are scans of two lots of the L-malic acid salt of the compound of Formula I. **Fig. 18I** is a differential scanning calorimetry scan of the L-malic acid salt (Lot A). **Fig. 18J** is a thermogravimetric analysis scan of the L-malic acid salt (Lot A). **Fig. 18K** is a differential scanning calorimetry scan of the L-malic acid salt (Lot B). **Fig. 18L** is a thermogravimetric analysis scan of the L-malic acid salt (Lot B). **Fig. 18M** is an overlay of X-ray powder diffraction scans of the L-malic acid salts (Lot A and Lot B) and the freebase of the compound of Formula I.

[0064] **Figs. 19A-19F** are scans of polymorph Form 1 of the compound of Formula II. **Fig. 19A** is an X-ray powder diffraction scan of fully dried Form 1. **Fig. 19B** is a differential scanning calorimetry scan of Form 1. **Fig. 19C** is a thermogravimetric/differential thermal analysis scan of Form 1. **Fig. 19D** is a gravimetric vapor sorption isotherm of Form 1. **Fig. 19E** is a kinetic gravimetric vapor sorption scan of Form 1. **Fig. 19F** is a ^1H NMR spectrum of Form 1 in d_6 -DMSO.

[0065] **Figs. 20A-20E** are scans of polymorph Form 2 of the compound of Formula II. **Fig. 20A** shows X-ray powder diffraction scans of Form 2 (small scale slurry, large scale slurry, and fully dried). **Fig. 20B** is a differential scanning calorimetry scan of Form 2. **Fig. 20C** is a thermogravimetric/differential thermal analysis scan of Form 2. **Fig. 20D** is a gravimetric vapor sorption isotherm of Form 2. **Fig. 20E** is a kinetic gravimetric vapor sorption scan of Form 2.

[0066] **Figs. 21A-21F** are scans of polymorph Form 7 of the compound of Formula II. **Fig. 21A** shows X-ray powder diffraction scans of Form 7 (small scale slurry, large scale slurry, and fully dried). **Fig. 21B** is a differential scanning calorimetry scan of Form 7. **Fig. 21C** is a thermogravimetric/differential thermal analysis scan of Form 7. **Fig. 21D** is a gravimetric vapor sorption isotherm of Form 7. **Fig. 21E** is a kinetic gravimetric vapor sorption scan of Form 7. **Fig. 21F** is a ^1H NMR spectrum of Form 7 in d_6 -DMSO.

[0067] **Figs. 22A-22F** are scans of polymorph Form 8 of the compound of Formula II. **Fig. 22A** shows X-ray powder diffraction scans of Form 8 (small scale slurry, large scale slurry, and fully dried). **Fig. 22B** is a differential scanning calorimetry scan of Form 8. **Fig. 22C** is a thermogravimetric/differential thermal analysis scan of Form 8. **Fig. 22D** is a gravimetric vapor

sorption isotherm of Form 8. **Fig. 22E** is a kinetic gravimetric vapor sorption scan of Form 8. **Fig. 22F** is a ^1H NMR spectrum of Form 8 in d_6 -DMSO.

[0068] **Figs. 23A-23F** are scans of the phosphate salt of the compound of Formula II. **Fig. 23A** is an X-ray powder diffraction scan of the fully dried phosphate salt. **Fig. 23B** is a differential scanning calorimetry scan of the phosphate salt. **Fig. 23C** is a thermogravimetric/differential thermal analysis scan of the phosphate salt. **Fig. 23D** is a gravimetric vapor sorption isotherm of the phosphate salt. **Fig. 23E** is a kinetic gravimetric vapor sorption scan of the phosphate salt. **Fig. 23F** is a ^1H NMR spectrum of Form 1 in d_6 -DMSO.

[0069] **Figs. 24A-24B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with hydrochloric acid. **Fig. 24A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 24B** shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0070] **Figs. 25A-25B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with sulfuric acid. **Fig. 25A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 25B** shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0071] **Figs. 26A-26B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with p-toluene sulfonic acid. **Fig. 26A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 26B** shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0072] **Figs. 27A-27B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with methane sulfonic acid. **Fig. 27A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 27B** shows the scans of the compound of

Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0073] **Figs. 28A-28B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with naphthalene-2-sulfonic acid. **Fig. 28A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 28B** shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0074] **Figs. 29A-29B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with benzene sulfonic acid. **Fig. 29A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 29B** shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0075] **Figs. 30A-30B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with oxalic acid. **Fig. 30A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 30B** shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0076] **Figs. 31A-31B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with 2-hydroxyethanesulfonic acid. **Fig. 31A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 31B** shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0077] **Figs. 32A-32B** are X-ray powder diffraction scans from a salt screen of the compound of Formula II with L-aspartic acid. **Fig. 32A** shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). **Fig. 32B** shows the scans of the compound of

Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0078] Figs. 33A-33B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with maleic acid. Fig. 33A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 33B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0079] Figs. 34A-34B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with phosphoric acid. Fig. 34A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 34B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0080] Figs. 35A-35B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with ethanesulfonic acid. Fig. 35A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 35B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0081] Figs. 36A-36B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with L-glutamic acid. Fig. 36A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 36B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0082] Figs. 37A-37B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with L-tartaric acid. Fig. 37A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 37B shows the scans of the compound of

Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0083] Figs. 38A-38B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with fumaric acid. Fig. 38A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 38B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0084] Figs. 39A-39B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with citric acid. Fig. 39A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 39B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0085] Figs. 40A-40B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with D-glucuronic acid. Fig. 40A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 40B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0086] Figs. 41A-41B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with L-malic acid. Fig. 41A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 41B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0087] Figs. 42A-42B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with hippuric acid. Fig. 42A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 42B shows the scans of the compound of Formula

II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0088] Figs. 43A-43B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with D-gluconic acid. Fig. 43A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 43B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0089] Figs. 44A-44B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with L-lactic acid. Fig. 44A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 44B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0090] Figs. 45A-45B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with L-ascorbic acid. Fig. 45A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 45B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0091] Figs. 46A-46B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with benzoic acid. Fig. 46A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 46B shows the scans of the compound of Formula II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0092] Figs. 47A-47B are X-ray powder diffraction scans from a salt screen of the compound of Formula II with succinic acid. Fig. 47A shows the scans of the compound of Formula II in each solvent tested after the samples were temperature cycled between room temperature and 40°C in 4-hour cycles over 24 hours (post-cycling). Fig. 47B shows the scans of the compound of Formula

II in each solvent tested after overnight storage of the samples in an oven at 40°C and 75% relative humidity (post-stability).

[0093] **Fig. 48** is a thermogravimetric/differential thermal analysis scan of the sulfate salt of the compound of Formula II identified in the primary salt screen.

[0094] **Fig. 49** is a thermogravimetric/differential thermal analysis scan of the tosylate salt of the compound of Formula II identified in the primary salt screen.

[0095] **Fig. 50** is a thermogravimetric/differential thermal analysis scan of the naphthalene-2-sulfonate salt of the compound of Formula II identified in the primary salt screen.

[0096] **Fig. 51** is a thermogravimetric/differential thermal analysis scan of the oxalate salt (1,4-dioxane/10% water) of the compound of Formula II identified in the primary salt screen.

[0097] **Fig. 52** is a thermogravimetric/differential thermal analysis scan of the oxalate salt (evaporation) of the compound of Formula II identified in the primary salt screen.

[0098] **Fig. 53** is a thermogravimetric/differential thermal analysis scan of the phosphate salt (acetone/10% water) of the compound of Formula II identified in the primary salt screen.

[0099] **Fig. 54** is a thermogravimetric/differential thermal analysis scan of the phosphate salt (IPA/10% water) of the compound of Formula II identified in the primary salt screen.

[00100] **Fig. 55** is a thermogravimetric/differential thermal analysis scan of the tartrate salt of the compound of Formula II identified in the primary salt screen.

[00101] **Fig. 56** is a thermogravimetric/differential thermal analysis scan of the fumarate salt of the compound of Formula II identified in the primary salt screen.

[00102] **Fig. 57** shows X-ray powder diffraction scans of the observed solids from the solvents tested in the solvent solubility screen of Form I of Formula II.

[00103] **Figs. 58A-58D** show X-ray powder diffraction scans of the compound of Formula II after temperature cycling experiments in various solvents and storage at 40°C and 75% RH overnight.

[00104] **Fig. 59** shows X-ray powder diffraction scans of the compound of Formula II after evaporation experiments using various solvents.

[00105] **Fig. 60** shows X-ray powder diffraction scans of the compound of Formula II after crash-cooling experiments using various solvents.

[00106] **Fig. 61** shows X-ray powder diffraction scans of the compound of Formula II after anti-solvent experiments using various solvents.

[00107] Figs. 62A-62F are scans of the compound of Formula II. Fig. 62A is an X-ray powder diffraction scan of the compound of Formula II. Fig. 62B is a differential scanning calorimetry scan of the compound of Formula II. Fig. 62C is a thermogravimetric/differential thermal analysis scan of the compound of Formula II. Fig. 62D is a dynamic vapor sorption isotherm of the compound of Formula II. Fig. 62E is a kinetic dynamic vapor sorption scan of the compound of Formula II. Fig. 62F is a ¹H NMR spectrum of the compound of Formula II in d₆-DMSO.

[00108] Figs. 63A-63B are scans of the polymorph Form A of the compound of Formula III. Fig. 63A is an X-ray powder diffraction scan of the polymorph Form A of the compound of Formula III. Fig. 63B is a differential scanning calorimetry scan of the polymorph Form A of the compound of Formula III.

[00109] Figs. 64A-64B are the scans of polymorph Form A of the compound of Formula IV. Fig. 64A is an X-ray powder diffraction scan of polymorph Form A of the compound of Formula IV. Fig. 64B is a differential scanning calorimetry scan of polymorph Form A of the compound of Formula IV.

[00110] Figs. 65A-B are the scans of polymorph Form B of the compound of Formula IV. Fig. 65A is an X-ray powder diffraction scan of polymorph Form B of the compound of Formula IV. Fig. 65B is a differential scanning calorimetry scan of polymorph Form B of the compound of Formula IV.

[00111] Fig. 66 is an overlay of the X-ray powder diffraction scans of polymorphs A and B of the compound of Formula IV.

DETAILED DESCRIPTION

[00112] 1. Definitions

[00113] The term “polymorph,” as used herein, refers to crystals of the same compound having different physical properties as a result of the order of the molecules in the crystal lattice. Different polymorphs of a single compound have one or more different chemical, physical, mechanical, electrical, thermodynamic, and/or biological properties from each other. Differences in physical properties exhibited by polymorphs can affect pharmaceutical parameters such as storage stability, compressibility, density (important in composition and product manufacturing), dissolution rates (an important factor in determining bio-availability), solubility, melting point, chemical stability, physical stability, powder flowability, water sorption, compaction, and particle morphology.

Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical changes (*e.g.*, crystal changes on storage as a kinetically favored polymorph converts to a thermodynamically more stable polymorph) or both (*e.g.*, one polymorph is more hygroscopic than the other). As a result of solubility/dissolution differences, some transitions affect potency and/or toxicity. In addition, the physical properties of the crystal may be important in processing; for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (*i.e.*, particle shape and size distribution might be different between one polymorph relative to the other). “Polymorph”, as used herein, does not include amorphous forms of the compound. As used herein, “amorphous” refers to a noncrystalline form of a compound which can be a solid state form of the compound or a solubilized form of the compound. For example, “amorphous” refers to a compound (*e.g.*, a solid form of the compound) without a regularly repeating arrangement of molecules or external face planes.

[00114] The term “anhydrous,” as used herein, refers to a crystal form of the compound of Formula I-IV that has 1% or less by weight water. For example, 0.5% or less, 0.25% or less, or 0.1% or less by weight water.

[00115] The term “solvate” as used herein refers to a crystalline form of a compound of Formula I-IV, such as a polymorph form of the compound, where the crystal lattice comprises one or more solvents of crystallization.

[00116] The terms “hydrate” or “hydrated polymorph form” refer to a crystalline form of a compound of Formula I-IV, such as a polymorph form of the compound, where the crystal lattice comprises water. Unless specified otherwise, the term “hydrate” as used herein refers to a “stoichiometric hydrate.” A stoichiometric hydrate contains the water molecules as an integral part of the crystal lattice, where removal of the water molecules will cause instability of the crystal network. In comparison, a non-stoichiometric hydrate comprises water, but changes in the water content does not cause significant changes to the crystal structure. During drying of non-stoichiometric hydrates, a considerable proportion of water can be removed without significantly disturbing the crystal network, and the crystals can subsequently rehydrate to give the initial non-stoichiometric hydrated crystalline form. Unlike stoichiometric hydrates, the dehydration and rehydration of non-stoichiometric hydrates is not accompanied by a phase transition, and thus all

hydration states of a non-stoichiometric hydrate represent the same crystal form.

[00117] “Purity,” when used in reference to a composition including a polymorph of a compound of Formula I-IV, refers to the percentage of one specific polymorph form relative to another polymorph form or an amorphous form of a compound of Formula I-IV in the referenced composition. For example, a composition comprising polymorph Form 1 having a purity of 90% would comprise 90 weight parts Form 1 and 10 weight parts of other polymorph and/or amorphous forms of the compound of Formula I-IV.

[00118] As used herein, a compound or composition is “substantially free of” one or more other components if the compound or composition contains no significant amount of such other components. For example, the composition can contain less than 5%, 4%, 3%, 2%, or 1% by weight of other components. Such components can include starting materials, residual solvents, or any other impurities that can result from the preparation of and/or isolation of the compounds and compositions provided herein. In some embodiments, a polymorph form provided herein is substantially free of other polymorph forms. In some embodiments, a particular polymorph of the compound of Formula I-IV is “substantially free” of other polymorphs if the particular polymorph constitutes at least about 95% by weight of the compound of Formula I-IV present. In some embodiments, a particular polymorph of the compound of Formula I-IV is “substantially free” of other polymorphs if the particular polymorph constitutes at least about 97%, about 98%, about 99%, or about 99.5% by weight of the compound of Formula I-IV present. In certain embodiments, a particular polymorph of the compound of Formula I-IV is “substantially free” of water if the amount of water constitutes no more than about 2%, about 1%, or about 0.5% by weight of the polymorph.

[00119] As used herein, “substantially pure,” when used in reference to a polymorph form of the compound of Formula I-IV, means a sample of a polymorph form of the compound having a purity greater than 90%, including greater than 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, and 99%, and also including equal to about 100% of the compound, based on the weight of the compound. The remaining material comprises other form(s) of the compound, and/or reaction impurities and/or processing impurities arising from its preparation. For example, a polymorph form of the compound of Formula I-IV may be deemed substantially pure in that it has a purity greater than 90% of a polymorph form of the compound of Formula I-IV, as measured by means that are at this time known and generally accepted in the art, where the remaining less than 10%

of material comprises other form(s) of the compound of Formula I-IV and/or reaction impurities and/or processing impurities. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, or infrared spectroscopy.

[00120] The term “about” preceding a value for DSC, TGA, TG, or DTA, which are reported as degrees Celsius, have an allowable variability of $\pm 5^{\circ}\text{C}$.

[00121] To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that when a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

[00122] “Room temperature” or “RT” refers to the ambient temperature of a typical laboratory, which is typically around 25°C .

[00123] As used herein, the terms “subject,” “individual,” or “patient,” used interchangeably, refer to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having a cancer with dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (a RET-associated cancer) (*e.g.*, as determined using a regulatory agency-approved, *e.g.*, FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (*e.g.*, as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (*e.g.*, identified as positive using a regulatory agency-approved, *e.g.*, FDA-approved, assay or kit). The subject can be a subject whose tumors have dysregulation of a RET gene, a RET protein, or expression or activity, or a level of the same (*e.g.*, where the tumor is identified as such using a regulatory agency-approved, *e.g.*, FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a RET-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (and optionally the clinical record indicates

that the subject should be treated with any of the compositions provided herein). In some embodiments, the patient is a pediatric patient.

[00124] The term “pediatric patient” as used herein refers to a patient under the age of 21 years at the time of diagnosis or treatment. The term “pediatric” can be further divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE, *Textbook of Pediatrics*, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, *et al.*, *Rudolph's Pediatrics*, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR, *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

[00125] As used herein, the terms “treat” or “treatment” refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (*e.g.*, one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment.

[00126] The term “administration” or “administering” refers to a method of giving a dosage of a compound or pharmaceutical composition to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian. The preferred method of administration can vary depending on

various factors, *e.g.*, the components of the pharmaceutical composition, the site of the disease, and the severity of the disease.

[00127] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well-known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions provided herein is contemplated. Supplementary active ingredients can also be incorporated into the compositions. In addition, various excipients, such as are commonly used in the art, can be included. These and other such compounds are described in the literature, *e.g.*, in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, *e.g.*, in Gilman *et al.* (Eds.) (2010); Goodman and Gilman’s: The Pharmacological Basis of Therapeutics, 12th Ed., The McGraw-Hill Companies.

[00128] By “therapeutically effective amount” or “pharmaceutically effective amount” of a compound as provided herein is an amount which is sufficient to achieve the desired effect and can vary according to the nature and severity of the disease condition, and the potency of the compound. A therapeutic effect is the relief, to some extent, of one or more of the symptoms of the disease, and can include curing a disease. “Curing” means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease can exist even after a cure is obtained (such as, *e.g.*, extensive tissue damage).

[00129] The term “RET-associated disease or disorder” as used herein refers to diseases or disorders associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein or RET kinase), or the expression or activity or level of any (*e.g.*, one or more) of the same (*e.g.*, any of the types of dysregulation of a RET gene, a RET kinase, a RET kinase domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of a RET-associated disease or disorder include, for example, cancer and gastrointestinal disorders such as irritable bowel syndrome (IBS).

[00130] The term “RET-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein or

RET kinase), or expression or activity, or level of any of the same. Non-limiting examples of a RET-associated cancer are described herein.

[00131] The phrase “dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same” refers to a genetic mutation (*e.g.*, a RET gene translocation that results in the expression of a fusion protein, a deletion in a RET gene that results in the expression of a RET protein that includes a deletion of at least one amino acid as compared to the wild-type RET protein, or a mutation in a RET gene that results in the expression of a RET protein with one or more point mutations, or an alternative spliced version of a RET mRNA that results in a RET protein that results in the deletion of at least one amino acid in the RET protein as compared to the wild-type RET protein), or a RET gene amplification that results in overexpression of a RET protein or an autocrine activity resulting from the overexpression of a RET gene a cell, that results in a pathogenic increase in the activity of a kinase domain of a RET protein (*e.g.*, a constitutively active kinase domain of a RET protein) in a cell. As another example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be a mutation in a RET gene that encodes a RET protein that is constitutively active or has increased activity as compared to a protein encoded by a RET gene that does not include the mutation. For example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of RET that includes a functional kinase domain, and a second portion of a partner protein (*i.e.*, that is not RET). In some examples, dysregulation of a RET gene, a RET protein, or expression or activity, can be a result of a gene translocation of one RET gene with another non-RET gene. Non-limiting examples of fusion proteins are described in Table 1. Non-limiting examples of RET kinase protein point mutations/insertions/deletions are described in Table 2. Additional examples of RET kinase protein mutations (*e.g.*, point mutations) are RET inhibitor resistance mutations. Non-limiting examples of RET inhibitor resistance mutations are described in Tables 3 and 4.

[00132] The term “wildtype” or “wild-type” describes a nucleic acid (*e.g.*, a RET gene or a RET mRNA) or protein (*e.g.*, a RET protein) that is found in a subject that does not have a RET-associated disease, *e.g.*, a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease), or is found in a cell or tissue from a subject that does not have a RET-associated disease,

e.g., a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease).

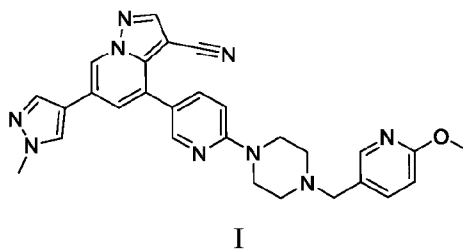
[00133] The term “regulatory agency” refers to a country’s agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[00134] 2. Polymorphs and pharmaceutically acceptable salts

[00135] The present disclosure relates to compounds of Formula I-IV and pharmaceutically acceptable salts thereof which exhibit rearranged during transfection (RET) kinase inhibition. In particular, provided herein are novel crystalline forms of 4-(6-(4-((6-methoxypyridin-3-yl)methyl)piperazin-1-yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula I); 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula II); 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-(6-methoxynicotinoyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula III); and 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (Formula IV), and pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising the compounds, processes for making the compounds, and the use of the compounds in therapy. More particularly, it relates to novel crystalline forms of Formula I-IV and pharmaceutically acceptable salts thereof useful in the treatment and prevention of diseases which can be treated with a RET kinase inhibitor, including RET-associated diseases and disorders.

[00136] Formula I

[00137] Provided herein is a compound of Formula I:



including pharmaceutically acceptable salts, amorphous, and polymorph forms thereof.

[00138] The compound of Formula I provided herein can be prepared using methods known and understood by those of ordinary skill in the art. For example, synthetic methods such as those described in U.S. Publication No. 2017/0096425 can be used.

[00139] Provided herein are polymorph forms of the compound of Formula I. The forms include, *e.g.*, free bases, solvates, hydrates, salts, and non-solvated forms of the compound of Formula I, including, for example, polymorph Form A. In some embodiments, the polymorph form of the compound of Formula I is a pharmaceutically acceptable salt. In some embodiments, the compound of Formula I is a chloride salt. In some embodiments, the compound of Formula I is a bromide salt. In some embodiments, the compound of Formula I is an L-malate salt. In some embodiments, the compound of Formula I is a D-malate salt.

[00140] *Form A*

[00141] One such polymorph is a polymorph known as Form A. Form A is a polymorph form of the compound of Formula I. In some embodiments, Form A has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 4.4 ± 0.2 , 14.6 ± 0.2 , and 18.3 ± 0.2 . In some embodiments, Form A has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 4.4 ± 0.2 , 13.5 ± 0.2 , 14.6 ± 0.2 , 18.3 ± 0.2 , and 18.8 ± 0.2 . In some embodiments, Form A has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 4.4 ± 0.2 , 13.5 ± 0.2 , 14.6 ± 0.2 , 17.4 ± 0.2 , 18.3 ± 0.2 , 18.8 ± 0.2 , 21.0 ± 0.2 , and 24.6 ± 0.2 . For example, in some embodiments, Form A has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 4.4 ± 0.2 , 13.5 ± 0.2 , 14.6 ± 0.2 , 17.4 ± 0.2 , 18.3 ± 0.2 , 18.8 ± 0.2 , 21.0 ± 0.2 , 22.5 ± 0.2 , 24.6 ± 0.2 , and 27.7 ± 0.2 .

[00142] In some embodiments, provided herein is a composition comprising polymorph Form A. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula I. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula I. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the

compound of Formula I. For example, the composition can contain less than about 15% of amorphous form.

[00143] In some embodiments, provided herein is polymorph Form A that exhibits an endotherm that is observed between about 185-195°C, *e.g.*, about 192.8°C, as measured by DSC related to sorbed water. In some embodiments, provided herein is polymorph Form A that exhibits an endotherm that is observed between about 220-230°C, *e.g.*, about 226.7°C, as measured by DSC related to sorbed water.

[00144] In some embodiments, provided herein is polymorph Form A that exhibits a weight loss of about 1.1% from the onset of heating to about 238°C, as measured by TGA.

[00145] Provided herein are methods of preparing polymorph Form A. In some embodiments, polymorph Form A of the compound of Formula I is prepared by contacting 6-(-1-methyl-1H-pyrazol-4-yl)-4-(6-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile tetrahydrochloride, sodium triacetoxyborohydride, and triethylamine in a polar aprotic solvent. In some embodiments, the polar aprotic solvent is DMSO. In some embodiments, the method further comprises heating a slurry comprising 6-(-1-methyl-1H-pyrazol-4-yl)-4-(6-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile tetrahydrochloride, sodium triacetoxyborohydride, trimethylamine, and DMSO to about 30°C. In some embodiments, the method further comprises heating the slurry for about 10 hours to about 15 hours, *e.g.*, about 13 hours. In some embodiments, the method further comprises cooling the slurry to about 19°C after about 13 hours of heating at about 30°C. In some embodiments, the method further comprises adding water to the slurry. For example, the method can further comprise adding 2 volumes of water to the slurry. In some embodiments, the method comprises ageing a composition comprising the slurry and water. In some embodiments, the method comprises ageing a composition comprising the slurry and water for about 1 hour to about 10 hours, *e.g.*, about 3.5 hours. In some embodiments, the method comprises isolating the solid through filtration. In some embodiments, the solid is dried. In some embodiments, the solid is dried under vacuum. In some embodiments, the solid is dried at about 45°C.

[00146] *Salts of Formula I*

[00147] In some embodiments, the compound of Formula I is a pharmaceutically acceptable salt. For example, pharmaceutically acceptable salts of the compound of Formula I can include,

but are not limited to, chloride, bromide, sulfate, citrate, L-tartrate, D-tartrate, acetate, L-malate, D-malate, benzoate, propionate, and maleate salts. In some embodiments, the compound of Formula I is a chloride salt. In some embodiments, the chloride salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of dichloromethane and ethanol. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the ratio of dichloromethane and ethanol is about 1:1 by volume. In some embodiments, the chloride salt is prepared in dimethylacetamide. In some embodiments, the compound of Formula I is a bromide salt. In some embodiments, the bromide salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of dichloromethane and ethanol. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the bromide salt is prepared in dimethylacetamide. In some embodiments, the compound of Formula I is a sulfate salt. In some embodiments, the sulfate salt is prepared in a mixture of solvents. In some embodiments, the sulfate salt is prepared in a mixture of dichloromethane and ethanol. In some embodiments, the ratio of dichloromethane and ethanol is about 4:1 by volume. In some embodiments, the compound of Formula I is a citrate salt. In some embodiments, the citrate salt is prepared in dichloromethane. In some embodiments, the compound of Formula I is an L-tartrate salt. In some embodiments, the L-tartrate salt is prepared in dichloromethane. In some embodiments, the compound of Formula I is a D-tartrate salt. In some embodiments, the D-tartrate salt is prepared in dichloromethane. In some embodiments, the compound of Formula I is an acetate salt. In some embodiments, the acetate salt is prepared in dichloromethane. In some embodiments, the compound of Formula I is an L-malate salt. In some embodiments, the L-malate salt is prepared in dichloromethane. In some embodiments, the L-malate salt is prepared in a mixture of solvents. In some embodiments, the L-malate salt is prepared in a mixture of dichloromethane and ethanol. In some embodiments, the ratio of dichloromethane and ethanol is about 6:1 by volume. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the ratio of dichloromethane and ethanol is about 3.3:1 by volume. In some embodiments, the compound of Formula I is a D-malate salt. In some embodiments, the D-malate salt is prepared in dichloromethane. In some embodiments, the D-malate salt is prepared in a mixture of solvents. In some embodiments, the D-malate salt is prepared in a mixture of dichloromethane and ethanol. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the compound of

Formula I is a benzoate salt. In some embodiments, the benzoate salt is prepared in dichloromethane. In some embodiments, the compound of Formula I is a propionate salt. In some embodiments, the propionate salt is prepared in dichloromethane. In some embodiments, the compound of Formula I is a maleate salt. In some embodiments, the maleate salt is prepared in dichloromethane.

[00148] Provided herein is a chloride salt of the compound of Formula I. In some embodiments, the chloride salt has a ratio of about 1.1:1, Cl:free base.

[00149] In some embodiments, provided herein is a composition comprising the chloride salt of the compound of Formula I. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula I. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula I. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula I.

[00150] In some embodiments, provided herein is a chloride salt of the compound of Formula I that exhibits an endotherm that is observed between about 230-245°C, *e.g.*, about 241°C or 234°C, as measured by DSC related to sorbed water. In some embodiments, provided herein is a chloride salt of the compound of Formula I that exhibits a melting point of about 241°C, as measured by DSC.

[00151] In some embodiments, the chloride salt of the compound of Formula I undergoes a mass loss of about 7.4% from the onset of heating to about 255°C, as measured by TGA.

[00152] Provided herein are methods of preparing a chloride salt of the compound of Formula I. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula I in a mixture of dichloromethane and ethanol and adding a hydrochloric acid solution to the mixture to generate the chloride salt as a residual solid. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the ratio of dichloromethane and ethanol is about 1:1 by volume. In some embodiments, the method

comprises slurring a composition comprising the compound of Formula I in dimethylacetamide and adding a hydrochloric acid solution to the mixture to generate the chloride salt as a residual solid. In some embodiments, the hydrochloric acid is added in a water solution. In some embodiments, the solvent is used in about 46 volumes. In some embodiments, the solvent is used in about 50 volumes. In some embodiments, the solvent is used in about 75 volumes. In some embodiments, the slurry is temperature cycled between about 0°C and about RT. In some embodiments, the slurry is temperature cycled between about 30°C and about RT. In some embodiments, the slurry is temperature cycled between about 40°C and about RT. In some embodiments, the method comprises adding MTBE to the slurry. In some embodiments, the method comprises adding about 125 volumes of MTBE. In some embodiments, the method comprises ageing the slurry. In some embodiments, the method comprises ageing the slurry for about 3 hours. In some embodiments, the method comprises ageing the slurry for about 13 hours. In some embodiments, the method comprises ageing the slurry for about 20 hours to about 40 hours, *e.g.*, about 30 hours. In some embodiments, the method comprises stirring the slurry. In some embodiments, the method comprises isolating the solid through filtration.

[00153] Provided herein is a bromide salt of the compound of Formula I. In some embodiments, the bromide salt has a ratio of about 1.1:1, Br:free base.

[00154] In some embodiments, provided herein is a composition comprising the bromide salt of the compound of Formula I. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula I. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula I. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula I.

[00155] In some embodiments, provided herein is a bromide salt of the compound of Formula I that exhibits an endotherm that is observed between about 235-250°C, *e.g.*, about 238°C, as measured by DSC related to sorbed water. In some embodiments, provided herein is a bromide

salt of the compound of Formula I that exhibits an endotherm that is observed between about 220-235°C, *e.g.*, about 225°C, as measured by DSC related to sorbed water. In some embodiments, provided herein is a bromide salt of the compound of Formula I that exhibits a melting point of about 225°C, as measured by DSC. In some embodiments, provided herein is a bromide salt of the compound of Formula I that exhibits a melting point of about 238°C, as measured by DSC.

[00156] In some embodiments, the bromide salt of the compound of Formula I undergoes a mass loss of about 10.3% from the onset of heating to about 255°C, as measured by TGA.

[00157] Provided herein are methods of preparing a bromide salt of the compound of Formula I. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula I in a mixture of dichloromethane and ethanol and adding a hydrobromic acid solution to the mixture to generate the bromide salt as a residual solid. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula I in dimethylacetamide and adding a hydrobromic acid solution to the mixture to generate the bromide salt as a residual solid. In some embodiments, the hydrobromic acid is added in a water solution. In some embodiments, the solvent is used in 46 volumes. In some embodiments, the solvent is used in about 50 volumes. In some embodiments, the slurry is temperature cycled between around about 0°C and about RT. In some embodiments, the slurry is temperature cycled between around about 30°C and about RT. In some embodiments, the slurry is temperature cycled between around about 40°C and about RT. In some embodiments, the method comprises further comprises adding MTBE to the slurry. In some embodiments, the method comprises adding about 150 volumes of MTBE. In some embodiments, the method comprises ageing the slurry. In some embodiments, the method comprises ageing the slurry for about 1 hour. In some embodiments, the method comprises ageing the slurry for about 13 hours. In some embodiments, the method comprises ageing the slurry for about 10 hours to about 30 hours, *e.g.*, about 20 hours. In some embodiments, the method comprises isolating the solid through filtration.

[00158] Provided herein is an L-malate salt of the compound of Formula I. In some embodiments, the L-malate salt has a ratio of about 0.97:1, malate:free base.

[00159] In some embodiments, provided herein is a composition comprising the L-malate salt of the compound of Formula I. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the

composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula I. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula I. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula I.

[00160] In some embodiments, provided herein is an L-malate salt of the compound of Formula I that exhibits an endotherm that is observed between about 205-220°C, *e.g.*, about 208°C, as measured by DSC related to sorbed water. In some embodiments, provided herein is an L-malate salt of the compound of Formula I that exhibits a melting point of about 208°C, as measured by DSC.

[00161] In some embodiments, the L-malate salt of the compound of Formula I undergoes a mass loss of about 17.7% from the onset of heating to about 253°C, as measured by TGA.

[00162] Provided herein are methods of preparing an L-malate salt of the compound of Formula I. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula I in a mixture of dichloromethane and ethanol and adding an L-malic acid solution to the mixture to generate the L-malate salt as a residual solid. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the ratio of dichloromethane and ethanol is about 3.3:1 by volume. In some embodiments, the ratio of dichloromethane and ethanol is about 6:1 by volume. In some embodiments, the L-malic acid is added in an ethanol solution. In some embodiments, the solvent is used in about 46 volumes. In some embodiments, the solvent is used in about 26 volumes. In some embodiments, the slurry is temperature cycled between about 0°C and about RT. In some embodiments, the method comprises ageing the slurry. In some embodiments, the method comprises ageing the slurry for about 5 hours to about 24 hours, *e.g.*, about 13 hours. In some embodiments, the method comprises ageing the slurry for about 10 hours to about 30 hours, *e.g.*, about 20 hours. In some embodiments, the method comprises stirring the slurry. In some embodiments, the method comprises isolating the solid through filtration.

[00163] Provided herein is an D-malate salt of the compound of Formula I. In some

embodiments, the D-malate salt has a ratio of about 0.97:1, malate:free base.

[00164] In some embodiments, provided herein is a composition comprising the D-malate salt of the compound of Formula I. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula I. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula I. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula I.

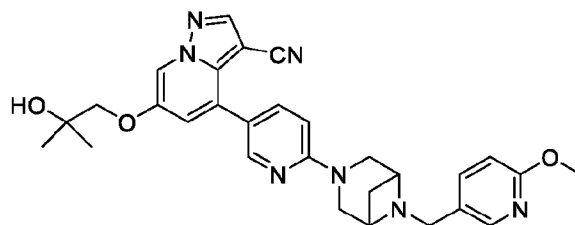
[00165] In some embodiments, provided herein is a D-malate salt of the compound of Formula I that exhibits an endotherm that is observed between about 205-215°C, *e.g.*, about 208°C, as measured by DSC related to sorbed water. In some embodiments, provided herein is an D-malate salt of the compound of Formula I that exhibits a melting point of about 209°C, as measured by DSC.

[00166] In some embodiments, the D-malate salt of the compound of Formula I undergoes a mass loss of about 18.4% from the onset of heating to before about 250°C, as measured by TGA.

[00167] Provided herein are methods of preparing a D-malate salt of the compound of Formula I. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula I in a mixture of dichloromethane and ethanol and adding a D-malic acid solution to the mixture to generate the D-malate salt as a residual solid. In some embodiments, the ratio of dichloromethane and ethanol is about 3.6:1 by volume. In some embodiments, the ratio of dichloromethane and ethanol is 3.3:1 by volume. In some embodiments, the D-malic acid is added in an ethanol solution. In some embodiments, the solvent is used in about 46 volumes. In some embodiments, the slurry is temperature cycled between about 0°C and about RT. In some embodiments, the method comprises ageing the slurry. In some embodiments, the method comprises ageing the slurry for about 13 hours. In some embodiments, the method comprises ageing the slurry for about 20 hours. In some embodiments, the method comprises isolating the solid through filtration.

[00168] Formula II

[00169] Provided herein is a compound of Formula II:



II

including pharmaceutically acceptable salts, amorphous, and polymorph forms thereof.

[00170] The compound of Formula II provided herein can be prepared using methods known and understood by those of ordinary skill in the art. For example, synthetic methods such as those described in U.S. Patent 10,112,942.

[00171] Provided herein are polymorph forms of the compound of Formula II. The forms include, *e.g.*, free bases, solvates, hydrates, salts, and non-solvated forms of the compound of Formula II, including, for example, polymorph Forms 1, 2, 7, and 8. In some embodiments, the polymorph form of the compound of Formula II is a pharmaceutically acceptable salt. In some embodiments, the compound of Formula II is a phosphate salt.

[00172] Form 1

[00173] One such polymorph is a polymorph known as Form 1. Form 1 is an anhydrous polymorph of the compound of Formula II. In some embodiments, Form 1 has an X-ray powder diffraction (XRPD or XRD) pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 16.5 ± 0.2 , 18.9 ± 0.2 , and 26.0 ± 0.2 . In some embodiments, Form 1 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 16.5 ± 0.2 , 18.9 ± 0.2 , 23.8 ± 0.2 , 25.3 ± 0.2 , and 26.0 ± 0.2 . In some embodiments, Form 1 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 16.5 ± 0.2 , 17.8 ± 0.2 , 18.9 ± 0.2 , 23.8 ± 0.2 , 25.3 ± 0.2 , 25.6 ± 0.2 , 26.0 ± 0.2 , and 28.3 ± 0.2 . For example, in some embodiments, Form 1 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 9.8 ± 0.2 , 16.5 ± 0.2 , 17.8 ± 0.2 , 18.9 ± 0.2 , 23.8 ± 0.2 , 25.0 ± 0.2 , 25.3 ± 0.2 , 25.6 ± 0.2 , 26.0 ± 0.2 , and 28.3 ± 0.2 .

[00174] In some embodiments, provided herein is a composition comprising polymorph Form 1. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula II. For example, in some embodiments, the composition is substantially free of other anhydrous forms of the compound of Formula II. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula II. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less by weight of one or more other forms of the compound of Formula II. For example, the composition can contain less than about 15% of Form 2, Form 7, Form 8, or a combination of two or more thereof.

[00175] In some embodiments, provided herein is polymorph Form 1 that exhibits an endotherm that is observed between about 185-200°C, *e.g.*, about 195°C, as measured by differential scanning calorimetry (DSC) related to sorbed water. In some embodiments, polymorph Form 1 exhibits an endothermic event that is observed between about 200-210°C, *e.g.*, about 207°C. In some embodiments, the endotherms are observed when using a scan rate of 10°C per minute.

[00176] In some embodiments, provided herein is polymorph Form 1 that exhibits an endothermic event observed from an onset of about 190°C, as measured by thermogravimetric/differential thermal analysis (TG/DTA). In some embodiments, polymorph Form 1 undergoes a mass loss of about 0.4% before about 200°C, *e.g.*, from about 190°C to about 200°C. In some embodiments, polymorph Form 1 exhibits an endothermic event from an onset of about 204°C. In some embodiments, the endothermic event is accompanied by a corresponding weight loss of about 0.2%.

[00177] Provided herein are methods of preparing polymorph Form 1. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula II in a solvent selected from the group consisting of 1,4-dioxane, 1-butanol, 1-propanol, acetone, anisole, chloroform, cyclohexane, cyclohexanone, dichloromethane, DMSO, ethanol, ethyl acetate, isopropyl alcohol, methyl ethyl ketone, methyl acetate, 2-ethoxyethanol, 2-methyl THF, methyl isobutyl ketone (MIBK), nitromethane, and THF to generate polymorph Form 1 as a residual solid.

In some embodiments, the solvent is ethyl acetate. In some embodiments, the solvent is in a mixture with water, for example the solvent can be a mixture of water and acetone or water and acetonitrile. In some embodiments, the water is present in an amount of about 20% by weight. In some embodiments, the water is present in an amount of about 50% by weight. In some embodiments, the slurry is temperature cycled between about 40°C and about RT. In some embodiments, the temperature cycling occurs between about 60 hours and about 84 hours, such as, *e.g.*, about 72 hours. In some embodiments, the method further comprises collecting the residual solid. In some embodiments, the residual solid is collected by filtration. In some embodiments, the method further comprises drying the residual solid, for example, under vacuum. In some embodiments, the drying is at a temperature of between about 30°C and about 50°C, such as, *e.g.*, about 40°C.

[00178] In some embodiments, a method of preparing a polymorph of Form 1 is provided. The method comprises providing a composition comprising the compound of Formula II in a solvent. In some embodiments, polymorph Form 1 can be prepared by evaporating the solvent from the composition comprising the compound of Formula II to generate polymorph Form 1 as a residual solid, where the solvent is selected from the group consisting of dichloromethane, DMSO, methyl acetate, 2-ethoxyethanol, nitromethane, and a mixture of acetonitrile and water (20%). In some embodiments, the method comprises evaporating the solvent from a composition comprising the compound of Formula II to generate a mixture of polymorph Form 1 and another polymorph form as a residual solid, where the solvent is selected from the group consisting of acetone, chloroform, and THF. In some embodiments, the residual solid is a mixture of Form 1 and Form 8.

[00179] In some embodiments, polymorph Form 1 can be prepared by cooling a solution comprising the compound of Formula II in acetone to a temperature of about 5°C to precipitate polymorph Form 1 as a residual solid. In some embodiments, the residual solid is a mixture of Form 1 and Form 8.

[00180] In some embodiments, polymorph Form 1 can be prepared by recrystallizing a composition comprising the compound of Formula II to generate polymorph Form 1, where the recrystallizing solvent is selected from the group consisting of a mixture of DMSO and water and a mixture of dichloromethane and heptane.

[00181] *Form 2*

[00182] Also provided herein is a polymorph known as Form 2. Form 2 is a hydrated polymorph form of the compound of Formula II. In some embodiments, Form 2 has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 15.1 ± 0.2 , 17.8 ± 0.2 , and 24.2 ± 0.2 . In some embodiments, Form 2 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 15.1 ± 0.2 , 17.8 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , and 24.2 ± 0.2 . In some embodiments, Form 2 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , and 24.6 ± 0.2 . For example, in some embodiments, Form 2 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 6.2 ± 0.2 , 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , 24.6 ± 0.2 , and 31.2 ± 0.2 .

[00183] In some embodiments, provided herein is a composition comprising polymorph Form 2. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula II. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula II. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula II. For example, the composition can contain less than about 15% of Form 1, Form 7, Form 8, or a combination of two or more thereof.

[00184] In some embodiments, provided herein is polymorph Form 2 that exhibits an endotherm that is observed between about 190-200°C, *e.g.*, about 197.5°C, as measured by DSC related to sorbed water. In some embodiments, polymorph Form 2 exhibits an endothermic event that is observed between about 200-210°C, *e.g.*, about 207.5°C. In some embodiments, the endotherms are observed when using a scan rate of 10°C per minute.

[00185] In some embodiments, provided herein is polymorph Form 2 that exhibits a weight loss of about 0.7% from the onset of heating to about 165°C, as measured by TG/DTA. In some embodiment, polymorph Form 2 exhibits an endothermic event observed from an onset of around 194°C. In some embodiments, polymorph Form 2 undergoes a mass loss of about 0.2% before

about 200°C, *e.g.*, from about 194°C to about 200°C. In some embodiments, polymorph Form 2 exhibits an endothermic event from an onset of about 205°C.

[00186] Provided herein are methods of preparing polymorph Form 2. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula II in a mixture of ethanol and water to generate polymorph Form 2 as a residual solid. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the slurry is temperature cycled between about 40°C and about RT. In some embodiments, the temperature cycling occurs between about 60 hours and about 84 hours, such as, *e.g.*, about 72 hours. In some embodiments, the method further comprises collecting the residual solid. In some embodiments, the residual solid is collected by filtration. In some embodiments, the residual solid is dried. In some embodiments, the residual solid is dried on the filter bed.

[00187] *Form 7*

[00188] Provided herein is a polymorph known as Form 7. Form 7 is a hydrated polymorph form of the compound of Formula II. In some embodiments, Form 7 has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 16.6 $\pm$ 0.2, 18.0 $\pm$ 0.2, and 19.9 $\pm$ 0.2. In some embodiments, Form 7 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 16.6 $\pm$ 0.2, 18.0 $\pm$ 0.2, 19.3 $\pm$ 0.2, 19.9 $\pm$ 0.2, and 23.3 $\pm$ 0.2. In some embodiments, Form 7 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 16.6 $\pm$ 0.2, 17.3 $\pm$ 0.2, 18.0 $\pm$ 0.2, 19.0 $\pm$ 0.2, 19.3 $\pm$ 0.2, 19.9 $\pm$ 0.2, 23.3 $\pm$ 0.2, and 25.1 $\pm$ 0.2. For example, in some embodiments, Form 7 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 15.8 $\pm$ 0.2, 16.6 $\pm$ 0.2, 17.3 $\pm$ 0.2, 18.0 $\pm$ 0.2, 19.0 $\pm$ 0.2, 19.3 $\pm$ 0.2, 19.91 $\pm$ 0.2, 21.4 $\pm$ 0.2, 23.3 $\pm$ 0.2, and 25.1 $\pm$ 0.2.

[00189] In some embodiments, provided herein is a composition comprising polymorph Form 7. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula II. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula II. For example, the composition can contain less than 14%, 13%, 12%,

11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula II. For example, the composition can contain less than about 15% of Form 1, Form 2, Form 8, or a combination of two or more thereof.

[00190] In some embodiments, provided herein is polymorph Form 7 that exhibits an endotherm that is observed between about 145-155°C, *e.g.*, about 150°C, as measured by DSC related to sorbed water. In some embodiments, polymorph Form 7 exhibits an endotherm that is observed between about 190-205°C, *e.g.*, about 201°C. In some embodiments, polymorph Form 7 exhibits an endothermic event that is observed between about 205-210°C, *e.g.*, about 207°C. In some embodiments, the endotherms are observed when using a scan rate of 10°C per minute.

[00191] In some embodiments, provided herein is polymorph Form 7 that exhibits an endothermic event observed from an onset of about 147°C, as measured by TG/DTA. In some embodiments, polymorph Form 7 undergoes a weight loss of about 7% before about 150°C, *e.g.*, from about 145°C to about 155°C. In some embodiments, the weight loss is the loss of solvent. In some embodiments, the weight loss is equal to about two equivalents of solvent as compared to the amount of compound present in the sample. In some embodiments, the solvent is water. In some embodiments, polymorph Form 7 exhibits an endothermic event observed from an onset of about 196°C. In some embodiments, polymorph Form 7 dehydrates upon heating to become polymorph Form 1. In some embodiments, the endothermic event relates to the transition observed in Form 1. In some embodiments, the transition relates to the endothermic event of Form 1 observed from an onset of about 206°C.

[00192] Provided herein are methods of preparing polymorph Form 7. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula II in a mixture of 1,4-dioxane and water to generate polymorph Form 7 as a residual solid. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the slurry is temperature cycled between about 40°C and about RT. In some embodiments, the temperature cycling occurs between about 60 hours and about 84 hours, such as, *e.g.*, about 72 hours. In some embodiments, the method further comprises collecting the residual solid. In some embodiments, the residual solid is collected by filtration. In some embodiments, the residual solid is dried. In some embodiments, the residual solid is dried on the filter bed.

[00193] *Form 8*

[00194] Provided herein is a polymorph known as Form 8. Form 8 is a solvated polymorph form of the compound of Formula II. Polymorph Form 8 is an isopropyl alcohol solvate polymorph form of the compound of Formula II. In some embodiments, Form 8 has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 15.1 ± 0.2 , 17.8 ± 0.2 , and 24.2 ± 0.2 . In some embodiments, Form 8 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 15.1 ± 0.2 , 17.8 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , and 24.2 ± 0.2 . In some embodiments, Form 8 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , and 24.6 ± 0.2 . For example, in some embodiments, Form 8 has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 6.2 ± 0.2 , 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , 24.6 ± 0.2 , and 31.2 ± 0.2 .

[00195] In some embodiments, provided herein is a composition comprising polymorph Form 8. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula II. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula II. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula II. For example, the composition can contain less than about 15% of Form 1, Form 2, Form 7, or a combination of two or more thereof.

[00196] In some embodiments, provided herein is polymorph Form 8 that exhibits an endotherm that is observed between about 165-175°C, *e.g.*, about 172°C, as measured by DSC related to sorbed water. In some embodiments, polymorph Form 8 exhibits an endotherm that is observed between about 185-200°C, *e.g.*, about 196°C. In some embodiments, polymorph Form 8 exhibits an endothermic event that is observed between about 200-210°C, *e.g.*, about 206°C. In some embodiments, the endotherms are observed when using a scan rate of 10°C per minute.

[00197] In some embodiments, provided herein is polymorph Form 8 that exhibits an endothermic event observed at about 165°C, as measured by TG/DTA. In some embodiments,

polymorph Form 8 undergoes a weight loss of about 4% before about 165°C. In some embodiments, the weight loss is the loss of solvent. In some embodiments, the weight loss is equal to about 0.5 equivalents of solvent. In some embodiments, the solvent is IPA. In some embodiments, polymorph Form 8 exhibits an endothermic event observed from an onset of about 191°C. In some embodiments, the endothermic event relates to the transition observed in Form 1. In some embodiments, the transition relates to the endothermic event of Form 1 observed from an onset of about 205°C.

[00198] Provided herein are methods of preparing polymorph Form 8. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula II in a solvent selected from the group consisting of IPA and 1-propanol to generate polymorph Form 8 as a residual solid. In some embodiments, the slurry is temperature cycled between about 40°C and about RT. In some embodiments, the temperature cycling occurs between about 60 hours and about 84 hours, such as, *e.g.*, about 72 hours. In some embodiments, the method further comprises collecting the residual solid. In some embodiments, the residual solid is collected by filtration. In some embodiments, the method further comprises drying the residual solid, for example, under vacuum. In some embodiments, the drying is at a temperature of between about 30°C and about 50°C, such as, *e.g.*, about 40°C.

[00199] In some embodiments, a method of preparing a polymorph of Form 8 is provided. The method comprises providing a composition comprising the compound of Formula II in a solvent. In some embodiments, the method comprises evaporating the solvent from the composition comprising the compound of Formula II, including amorphous and polymorph forms thereof to generate a mixture of polymorph Form 8 and another polymorph form as a residual solid. In some embodiments, the residual solid is a mixture of polymorph Form 8 and polymorph Form 1. In some embodiments, the solvent is acetone. In some embodiments, the solvent is chloroform. In some embodiments, the solvent is THF.

[00200] *Salts of Formula II*

[00201] In some embodiments, the compound of Formula II is a pharmaceutically acceptable salt. For example, pharmaceutically acceptable salts of the compound of Formula II can include, but are not limited to, sulfate, tosylate, naphthalene-2-sulfonate, oxalate, phosphate, tartrate, and fumarate salts. In some embodiments, the compound of Formula II is a sulfate salt. In some

embodiments, the sulfate salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of IPA and water. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the compound of Formula II is a tosylate salt. In some embodiments, the tosylate salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of acetone and water. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the compound of Formula II is a naphthalene-2-sulfonate salt. In some embodiments, the naphthalene-2-sulfonate salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of THF and water. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the compound of Formula II is an oxalate salt. In some embodiments, the oxalate salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of 1,4-dioxane and water. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the oxalate salt is prepared from evaporation from a mixture of solvents. In some embodiments, the solvent is a mixture of THF and water. In some embodiments, the compound of Formula II is a tartrate salt. In some embodiments, the tartrate salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of IPA and water. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the compound of Formula II is a fumarate salt. In some embodiments, the fumarate salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of THF and water. In some embodiments, the compound of Formula II is a phosphate salt. In some embodiments, the phosphate salt is prepared in a mixture of solvents. In some embodiments, the solvent is a mixture of acetone and water. In some embodiments, the solvent is a mixture of IPA and water. In some embodiments, the water is present in an amount of about 10% by weight.

[00202] Provided herein is a phosphate salt of the compound of Formula II. In some embodiments, the phosphate salt has a ratio of about 1.4:1, PO₄:free base. In some embodiments, the phosphate salt has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 3.6 ± 0.2 , 16.7 ± 0.2 , and 18.2 ± 0.2 . In some embodiments, the phosphate salt has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 3.6 ± 0.2 , 15.9 ± 0.2 , 16.7 ± 0.2 , 17.8 ± 0.2 , and 18.2 ± 0.2 . In some embodiments, the phosphate salt has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 3.6 ± 0.2 , 6.2 ± 0.2 , 15.9 ± 0.2 , 16.7 ± 0.2 , 17.8 ± 0.2 , 18.2 ± 0.2 , 20.3 ± 0.2 , and 25.5 ± 0.2 . For example, in some embodiments, the phosphate salt has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of

3.6±0.2, 6.2±0.2, 15.9±0.2, 16.7±0.2, 17.8±0.2, 18.2±0.2, 19.1±0.2, 20.3±0.2, 20.9±0.2, and 25.5±0.2.

[00203] In some embodiments, provided herein is a composition comprising the phosphate salt of the compound of Formula II. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula II. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula II. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula II.

[00204] In some embodiments, provided herein is a phosphate salt of the compound of Formula II that exhibits an endotherm that is observed between about 165-175°C, *e.g.*, about 170°C, as measured by DSC related to sorbed water. In some embodiments, the endotherm is observed when using a scan rate of 10°C per minute.

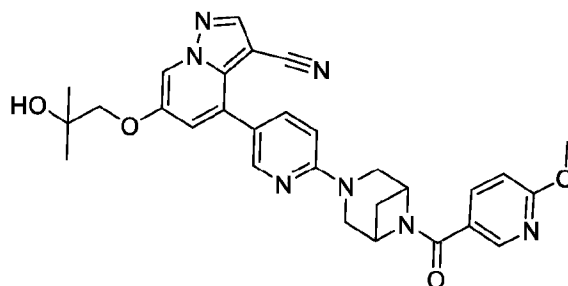
[00205] In some embodiments, provided herein is a phosphate salt of the compound of Formula II that exhibits a melting point of about 167°C, as measured by TG/DTA. In some embodiments, the phosphate salt of the compound of Formula II undergoes a mass loss of about 1.3% from the onset of heating to before about 150°C. In some embodiments, the phosphate salt of the compound of Formula II exhibits a second weight loss of about 1.2% from an onset of about 167°C.

[00206] Provided herein are methods of preparing a phosphate salt of the compound of Formula II. In some embodiments, the method comprises slurring a composition comprising the compound of Formula II in a mixture of water and IPA and adding a phosphoric acid solution to the mixture to generate the phosphate salt as a residual solid. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the acid is a 1M solution of phosphoric acid. In some embodiments, the slurry is temperature cycled between about 40°C and about RT. In some embodiments, the temperature cycling occurs between about 12 hours and about 48 hours, such as, *e.g.*, about 24 hours. In some embodiments, the method further comprises centrifuging the composition and collecting the residual solid. In some embodiments, the residual solid is washed

with a solvent. In some embodiments, the solvent is IPA. In some embodiments, the method further comprises drying the residual solid. In some embodiments, the residual solid is dried under vacuum. In some embodiments, the drying is at a temperature of between about 30°C and about 50°C, such as, *e.g.*, about 40°C.

[00207] Formula III

[00208] Provided herein is a compound of Formula III:



III

including pharmaceutically acceptable salts, amorphous, and polymorph forms thereof.

[00209] The compound of Formula III provided herein can be prepared using methods known and understood by those of ordinary skill in the art. For example, synthetic methods such as those described in U.S. Patent 10,112,942.

[00210] Provided herein are polymorph forms of the compound of Formula III. The forms include, *e.g.*, free bases, solvates, hydrates, salts, and non-solvated forms of the compound of Formula III, including, for example, polymorph Form A. In some embodiments, the polymorph form of the compound of Formula III is a pharmaceutically acceptable salt.

[00211] Form A

[00212] One such polymorph is a polymorph known as Form A. Form A is a polymorph form of the compound of Formula III. In some embodiments, Form A has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 17.3 ± 0.2 , 19.2 ± 0.2 , and 23.9 ± 0.2 . In some embodiments, Form A has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 4.7 ± 0.2 , 17.3 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , and 23.9 ± 0.2 . In some embodiments, Form A has an XRPD pattern

with at least peaks at 2θ values of 4.7 ± 0.2 , 6.8 ± 0.2 , 15.2 ± 0.2 , 17.3 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 20.2 ± 0.2 , and 23.9 ± 0.2 . For example, in some embodiments, Form A has an XRPD pattern with at least peaks at 2θ values of 4.7 ± 0.2 , 6.8 ± 0.2 , 13.4 ± 0.2 , 15.2 ± 0.2 , 15.9 ± 0.2 , 17.3 ± 0.2 , 18.8 ± 0.2 , 19.2 ± 0.2 , 20.2 ± 0.2 , and 23.9 ± 0.2 .

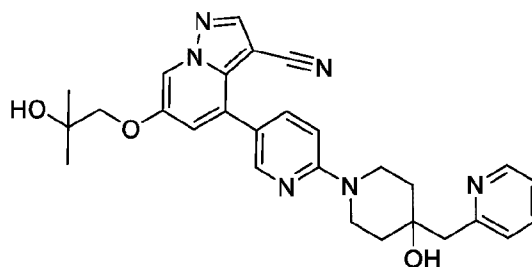
[00213] In some embodiments, provided herein is a composition comprising polymorph Form A. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula III. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula III. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula III. For example, the composition can contain less than about 15% of amorphous form.

[00214] In some embodiments, provided herein is polymorph Form A that exhibits an endotherm that is observed between about 135-150°C, *e.g.*, about 140.5°C or 146.6°C, as measured by DSC related to sorbed water.

[00215] Provided herein are methods of preparing polymorph Form A. In some embodiments, the method comprises dissolving the compound of Formula III in acetonitrile and adding water to generate polymorph Form A as a solid. In some embodiments, the method comprises heating a composition comprising the compound of Formula III and acetonitrile to reflux. In some embodiments, the ratio of acetonitrile and water is about 2:3 by volume. In some embodiments, the residual solid is collected by filtration. In some embodiments, the residual solid is dried. In some embodiments, the residual solid is dried under high vacuum. In some embodiments, the residual solid is dried at about 40-45 °C. In some embodiments, the residual solid is dried overnight.

[00216] Formula IV

[00217] Provided herein is a compound of Formula IV:



IV

including pharmaceutically acceptable salts, amorphous, and polymorph forms thereof.

[00218] The compound of Formula IV provided herein can be prepared using methods known and understood by those of ordinary skill in the art. For example, synthetic methods such as those described in U.S. Patent 10,144,734.

[00219] Provided herein are polymorph forms of the compound of Formula IV. The forms include, *e.g.*, free bases, solvates, hydrates, salts, and non-solvated forms of the compound of Formula IV, including, for example, polymorph Forms A and B. In some embodiments, the polymorph form of the compound of Formula IV is a pharmaceutically acceptable salt.

[00220] Form A

[00221] One such polymorph is a polymorph known as Form A. Form A is a polymorph form of the compound of Formula IV. In some embodiments, Form A has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 8.3 ± 0.2 , 16.3 ± 0.2 , and 21.9 ± 0.2 . In some embodiments, Form A has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 8.3 ± 0.2 , 16.3 ± 0.2 , 16.6 ± 0.2 , 19.4 ± 0.2 , and 21.9 ± 0.2 . In some embodiments, Form A has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 8.3 ± 0.2 , 16.3 ± 0.2 , 16.6 ± 0.2 , 19.4 ± 0.2 , 20.0 ± 0.2 , 20.5 ± 0.2 , 21.6 ± 0.2 , and 21.9 ± 0.2 . For example, in some embodiments, Form A has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 8.3 ± 0.2 , 16.3 ± 0.2 , 16.6 ± 0.2 , 18.1 ± 0.2 , 18.8 ± 0.2 , 19.4 ± 0.2 , 20.0 ± 0.2 , 20.5 ± 0.2 , 21.6 ± 0.2 , and 21.9 ± 0.2 .

[00222] In some embodiments, provided herein is a composition comprising polymorph Form A. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula IV. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula IV. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula IV. For example, the composition can contain less than about 15% of Form B, amorphous form, or a combination thereof.

[00223] In some embodiments, provided herein is polymorph Form A that exhibits an endotherm that is observed between about 145-155°C, *e.g.*, about 149.9°C, as measured by DSC related to sorbed water.

[00224] Provided herein are methods of preparing polymorph Form A. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula IV in a solvent selected from the group consisting of acetone, acetonitrile, 2-butanol, chloroform, ethanol, ethyl acetate, heptane, hexane, isopropanol, MTBE, DMSO, THF, water, and combinations thereof to generate polymorph Form A as a residual solid. In some embodiments, the solvent is acetone, 2-butanol, or acetonitrile. In some embodiments, the solvent is in a mixture with water, for example the solvent can be a mixture of water and acetone, water and ethanol, or water and DMSO. In some embodiments, the water is present in an amount of about 50% by weight. In some embodiments, the water is present in an amount of about 40% by weight. In some embodiments, the solvent is in a mixture with heptane, for example the solvent can be a mixture of chloroform and heptane or heptane and acetone. In some embodiments, the heptane is present in an amount of about 50% by weight. In some embodiments, the heptane is present in an amount of about 70% by weight. In some embodiments, Form A is prepared by adding an anti-solvent into a solution of the compound of Formula IV in a solvent. In some embodiments, the anti-solvent is heptane or water. In some embodiments, the solvent is DMSO and the anti-solvent is water. In some embodiments, the vapor of an anti-solvent is diffused into a solution of the compound of Formula IV. In some

embodiments, the method further comprises collecting the residual solid. In some embodiments, the residual solid is collected by filtration. In some embodiments, the method comprises washing the solid. In some embodiments, the method comprises washing the solid with water, MTBE, or a combination thereof. In some embodiments, the method further comprises drying the residual solid, for example, under vacuum.

[00225] *Form B*

[00226] One such polymorph is a polymorph known as Form B. Form B is a polymorph form of the compound of Formula IV. In some embodiments, Form B has an XRPD pattern, obtained with CuK α 1-radiation, with at least peaks at $^{\circ}2\theta$ values of 7.5 ± 0.2 , 13.7 ± 0.2 , and 16.9 ± 0.2 . In some embodiments, Form B has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 7.5 ± 0.2 , 9.7 ± 0.2 , 13.7 ± 0.2 , 16.9 ± 0.2 , and 19.9 ± 0.2 . In some embodiments, Form B has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 7.5 ± 0.2 , 9.7 ± 0.2 , 13.7 ± 0.2 , 14.5 ± 0.2 , 16.9 ± 0.2 , 19.4 ± 0.2 , 19.9 ± 0.2 , and 21.3 ± 0.2 . For example, in some embodiments, Form B has an XRPD pattern with at least peaks at $^{\circ}2\theta$ values of 7.5 ± 0.2 , 9.7 ± 0.2 , 9.9 ± 0.2 , 13.7 ± 0.2 , 14.5 ± 0.2 , 16.9 ± 0.2 , 19.4 ± 0.2 , 19.9 ± 0.2 , 21.3 ± 0.2 , and 27.4 ± 0.2 .

[00227] In some embodiments, provided herein is a composition comprising polymorph Form B. In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some embodiments, the composition is substantially free of other forms of the compound of Formula IV. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula IV. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the compound of Formula IV. For example, the composition can contain less than about 15% of Form A, amorphous form, or a combination thereof.

[00228] In some embodiments, provided herein is polymorph Form B that exhibits an endotherm that is observed between about 160-170°C, e.g., about 164.6°C, as measured by DSC related to sorbed water.

[00229] Provided herein are methods of preparing polymorph Form B. In some embodiments, the method comprises slurrying a composition comprising the compound of Formula IV in a mixture of ethanol and water to generate polymorph Form B as a residual solid. In some embodiments, the water is present in an amount of about 10% by weight. In some embodiments, the slurry is aged between about 24 and about 72 hours, *e.g.*, about 36 hours. In some embodiments, the method further comprises collecting the residual solid. In some embodiments, the residual solid is collected by filtration. In some embodiments, the residual solid is dried. In some embodiments, the residual solid is dried in a vacuum oven. In some embodiments, the residual solid is dried with nitrogen bleed. In some embodiments, the residual solid is dried at room temperature. In some embodiments, the residual solid is dried between about 10 and about 20 hours, *e.g.*, about 18 hours.

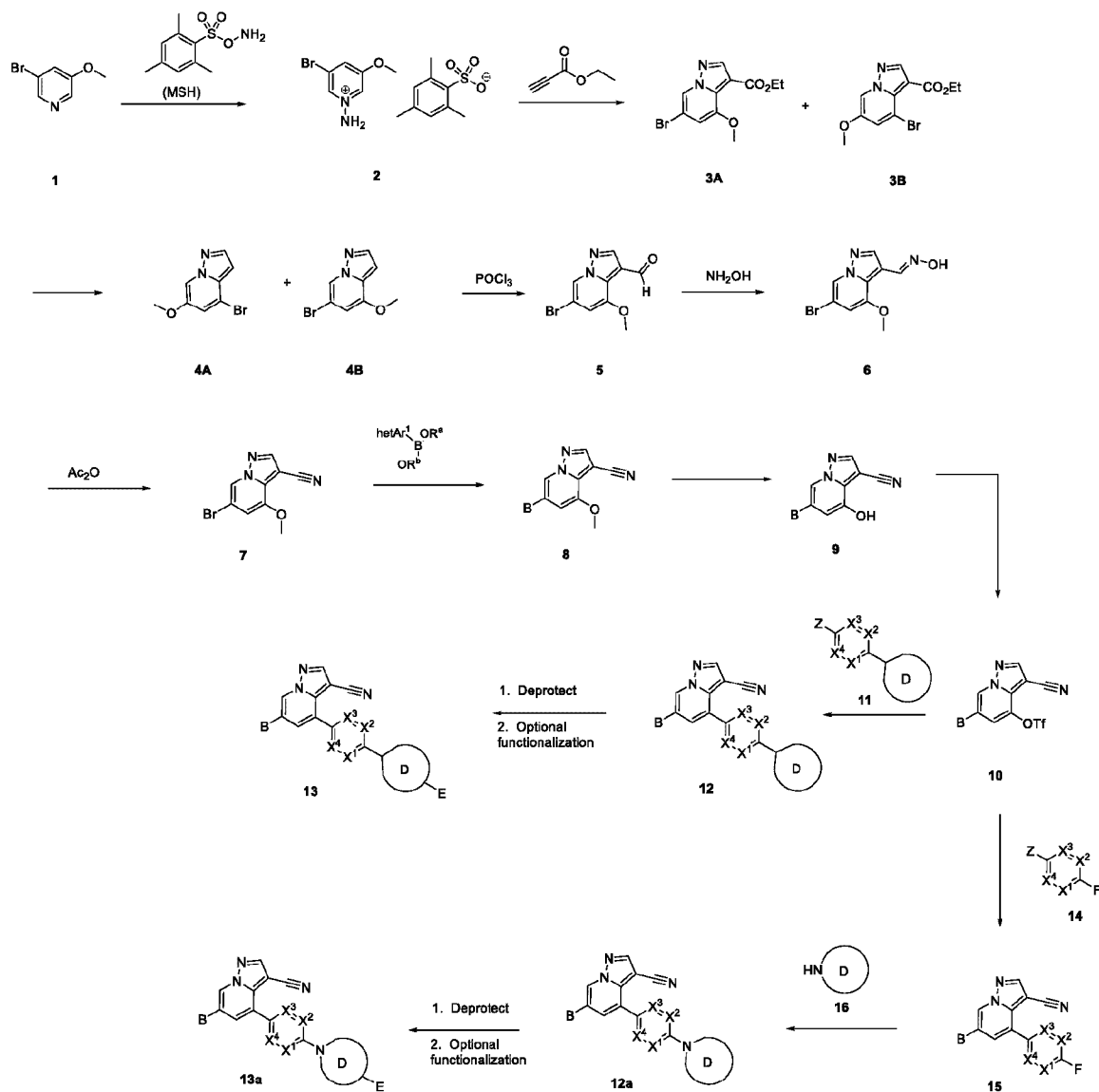
[00230] It will be understood that the 2-theta values of the XRPD patterns for the crystalline forms of the compound of Formula I-IV, *e.g.*, Forms A of Formula I, Forms 1, 2, 7, and 8 of Formula II, Form A of Formula III, or Forms A and B of Formula IV, and pharmaceutically acceptable salts thereof, *e.g.*, chloride salt, bromide salt, malate salt, and phosphate salt, can vary slightly from one instrument to another and also depending on variations in sample preparation and batch to batch variation, and so the values quoted are not to be construed as absolute. It will be understood that the peak positions in an XRPD pattern are reported in terms of angular positions (two theta) with an allowable variability of $\pm 0.2^\circ 2\theta$. The variability of $\pm 0.2^\circ 2\theta$ is intended to be used when comparing two powder XRPD patterns. In practice, if a diffraction pattern peak from one pattern is assigned a range of angular positions (two theta) which is the measured peak position $\pm 0.2^\circ$ and if those ranges of peak positions overlap, then the two peaks are considered to have the same angular position. For example, if a peak from one pattern is determined to have a position of $11.0^\circ 2\theta$, for comparison purposes the allowable variability allows the peak to be assigned a position in the range of 10.8° - $11.2^\circ 2\theta$. It will also be understood that the relative intensities of peaks can vary depending on orientation effects so that the intensities shown in the XRPD traces included herein are illustrative and not intended to be used for absolute comparison. It is to be further understood that for comparison purposes some variability in peak intensities from those shown in XRPD traces is allowed. Accordingly, it is to be understood that the phrase “substantially the same XRPD pattern as shown in Figure 1” means that for comparison purposes, at least 90% of the peaks shown in Figure 1 are present.

[00231] Compounds provided herein can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. That is, an atom, in particular when mentioned in relation to a compound according to Formula I-IV, comprises all isotopes and isotopic mixtures of that atom, such as naturally occurring isotopes with natural abundance. For example, when hydrogen is mentioned, it is understood to refer to ^1H , ^2H , ^3H or mixtures thereof; when carbon is mentioned, it is understood to refer to ^{12}C , ^{13}C , ^{14}C or mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{14}N , ^{15}N or mixtures thereof; and when oxygen is mentioned, it is understood to refer to ^{16}O , ^{17}O , ^{18}O or mixtures thereof. All isotopic variations of the compounds provided herein are intended to be encompassed within the scope of the present invention.

[00232] For illustrative purposes, Schemes 1-6 show general methods for preparing the compounds provided herein as well as key intermediates. For a more detailed description of the individual reaction steps, see, *e.g.*, U.S. Patent 10, 112,942.

Those skilled in the art will appreciate that other synthetic routes can be used to synthesize the compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions.

[00233] Scheme 1

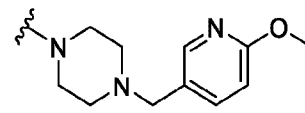


Scheme 1

[00234] Scheme 1 shows a general scheme for the synthesis of the compound of Formula I (shown as compound **13** and **13a** for Formula I in scheme 1), where B is 1-methyl-1H-pyrazole-

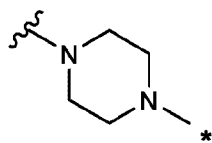
4-yl; X¹ is N; X², X³, and X⁴ are CH; and D and E are represented by

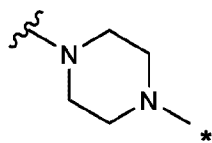
where the wavy line indicates the point of attachment to the ring comprising X¹, X², X³, and X⁴.



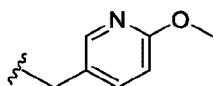
[00235] Compound **2** is obtained by treating MSH reagent with 3-bromo-5-methoxypyridine, which is commercially available. The aminating reagent O-mesitylsulfonylhydroxylamine (MSH) may be prepared as described in Mendiola, J., et al., Org. Process Res. Dev. 2009, 13(2), 263-267. Compound **2** may be reacted with ethyl propiolate to provide the pyrazolo[1,5-a]pyridine a mixture of compounds **3A** and **3B**, which typically are obtained in a ratio of approximately 2:1 to 9:1. The mixture of compounds **3A** and **3B** may be treated with 48% HBr at elevated temperatures, followed by recrystallization or chromatography purifications to isolate compound **4A** as the minor isomer and compound **4B** as the major isomer.

[00236] The isolated compound **4B** may be functionalized with a formyl group using POCl₃ followed by purification to provide compound **5**. The formyl group of compound **5** may be converted to an oxime group using NH₂OH to provide compound **6**. The oxime group of compound **6** may be converted to a nitrile group using acetic anhydride to provide compound **7**. The B group may be installed by treating compound **7** with a corresponding boronic ester having the formula hetAr¹-B(OR^a)(OR^b) where hetAr¹ is 1-methyl-1H-pyrazole-4-yl as defined in Formula I, using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, Pd₂(dba)₃, X-Phos and Na₂CO₃ in dioxane at elevated temperatures) to provide compound **8** where B is 1-methyl-1H-pyrazole-4-yl as defined in Formula I. The methoxy group of compound **8** may be converted to a hydroxy group by treating compound **8** with aluminum trichloride to provide compound **9**. The free hydroxy group of compound **9** may be converted to a triflate group by treating compound **9** with a triflating reagent, for example 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide to provide compound **10**. Compound **12** may be prepared by coupling compound **10** with the corresponding boronic ester

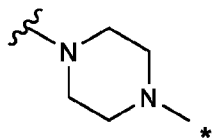


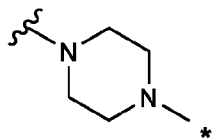
compound **11** where Ring D is , wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X¹, X², X³ and X⁴, and the asterisk indicates the point of attachment to P¹; X¹, X², X³ and X⁴ are as defined above; P¹ is an amino protecting group; Z is -B(OR^x)(OR^y) Z is -B(OR^a)(OR^b) and R^a and R^b are H or C1-C6 alkyl, or R^a and R^b together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with one to four C1-C3 alkyl groups, using appropriate palladium-catalyzed cross-coupling reaction

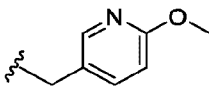
conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $\text{Pd}_2(\text{dba})_3$, X-Phos and Na_2CO_3 in dioxane at elevated temperatures). The protecting group on the D ring of compound **12** may be removed under standard conditions (for example, a Boc protecting group may be removed by treating compound **12** under acidic conditions, e.g., using HCl). The deprotected D ring may be functionalized (i.e., reacted or treated with an appropriate reagent) to introduce the E group under standard conditions such as described below to provide compound **13** where E is



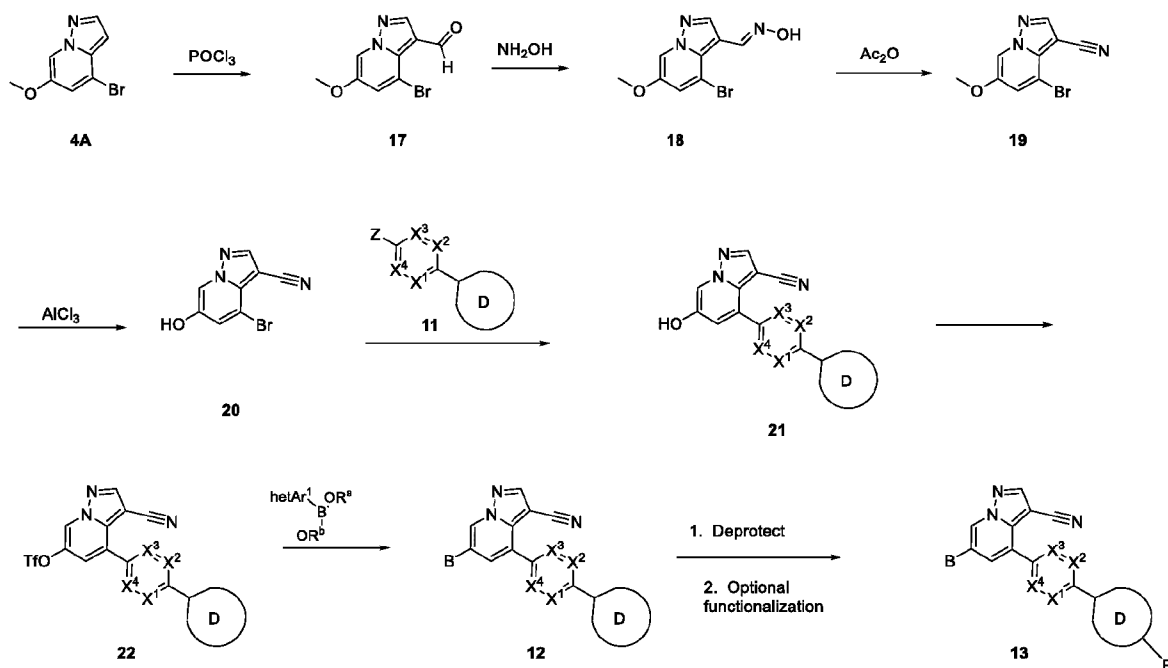
[00237] Alternatively, compound **10** may be coupled with compound **14** using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $\text{Pd}(\text{PPh}_3)_4$ and Na_2CO_3) to provide compound **15**. Compound **15** may be reacted with compound **16** under appropriate $\text{S}_\text{N}\text{Ar}$ conditions (for example, optionally in the presence of a base such as K_2CO_3 and at elevated temperature) to provide compound **12a**, wherein the D ring of



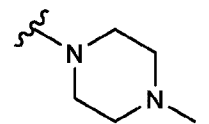
compound **16** is , wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1 , X^2 , X^3 and X^4 , and the asterisk indicates the point of attachment to P^1 ; X^1 , X^2 , X^3 and X^4 are as defined above; P^1 is an amino protecting group; Z is $-\text{B}(\text{OR}^x)(\text{OR}^y)$, the second nitrogen atom is protected with an appropriate amine protecting group prior to coupling. The protecting group if present on the D ring of compound **12a** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **12a** to acidic conditions, e.g., HCl). The deprotected D ring may be functionalized (i.e., reacted or treated with an appropriate reagent) to introduce the E group under standard conditions such as described below

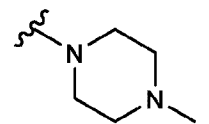
to provide compound **13a** where E is .

[00238] Scheme 2

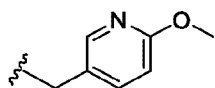


[00239] Scheme 2 shows an alternative route for the synthesis of compound **13**, wherein B, X^1 , X^2 , X^3 , X^4 , D and E are as defined in **Scheme 1**. Compound **4A** (prepared as in Scheme 1) may be functionalized with a formyl group using POCl_3 to provide compound **17**. The formyl group may be converted to an oxime group using NH_2OH to provide compound **18**. The oxime group may be converted to a nitrile group using acetic anhydride to provide compound **19**. The methoxy group of compound **19** may be converted to a hydroxy group by treating compound **19** with aluminum trichloride to provide compound **20**. Compound **21** may be prepared by coupling compound **20**

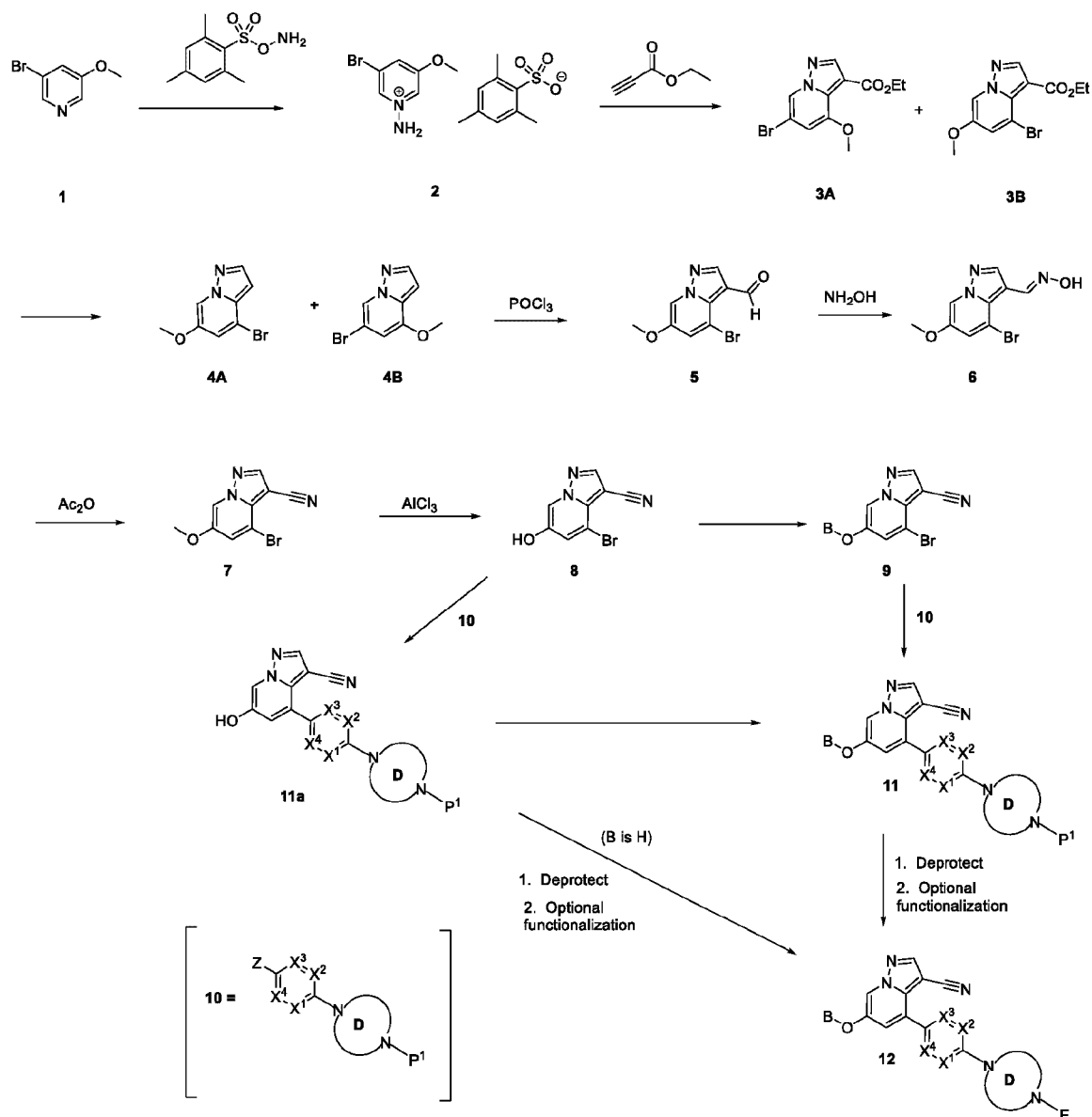


with the corresponding boronic ester compound **11** where Ring D is , wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1 , X^2 , X^3 and X^4 , and the asterisk indicates the point of attachment to P^1 ; X^1 , X^2 , X^3 and X^4 are as defined above; P^1 is an amino protecting group; Z is $-\text{B}(\text{OR}^a)(\text{OR}^b)$ and R^a and R^b are H or C1-C6 alkyl, or R^a and

R^b together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with one to four C1-C3 alkyl groups, using appropriate palladium-catalyzed cross-coupling reaction conditions, *e.g.*, Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures). The unsubstituted nitrogen atom of the D ring is protected with an appropriate amine protecting group prior to coupling. The free hydroxy group of compound **21** may be converted to a triflate group by treating compound **21** with a triflating reagent, for example 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide to provide compound **22**. The B group may be installed by treating compound **22** with the corresponding boronic ester having the formula $hetAr^1-B(OR^a)(OR^b)$ where $hetAr^1$ is 1-methyl-1H-pyrazole-4-yl as defined in Formula I and R^a and R^b are H or C1-C6 alkyl, or R^a and R^b together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with one to four C1-C3 alkyl groups, using appropriate palladium-catalyzed cross-coupling reaction conditions, *e.g.*, Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd_2(dba)_3$, X-Phos and Na_2CO_3 in dioxane at elevated temperatures) to provide compound **12** where B is 1-methyl-1H-pyrazole-4-yl as defined in Formula I. The protecting group if present on the D ring of compound **12** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **12** to acidic conditions, *e.g.*, HCl in propan-2-ol). The deprotected D ring may be functionalized (*i.e.*, reacted or treated with an appropriate reagent) to introduce the E group under standard conditions such as described below to provide compound **13** where E is



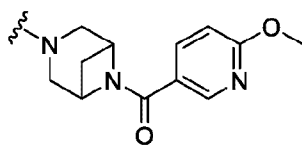
[00240] Scheme 3



[00241] **Scheme 3** shows a general scheme for the synthesis of the compound of Formula II or Formula III (shown as compound **12** for Formula II or III in **scheme 3**), where B is -CH₂C(CH₃)₂OH; X¹ is N; X², X³, and X⁴ are CH; and D and E are represented by



or

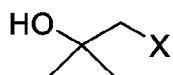


, respectively, where the wavy line

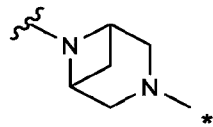
indicates the point of attachment to the ring comprising X^1 , X^2 , X^3 , and X^4 .

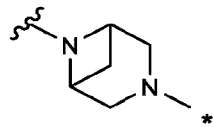
[00242] Compound **2** is obtained by treating commercially available 3-bromo-5-methoxypyridine (compound **1**) with O-(mesitylsulfonyl)hydroxylamine. The O-mesitylsulfonylhydroxylamine can be prepared as described in Mendiola *et al.*, Org. Process Res. Dev. (2009) 13(2):263-267. Compound **2** can be reacted with ethyl propiolate to provide a mixture of compounds **3A** and **3B**, which typically are obtained in a ratio of approximately 2:1 to 9:1, respectively. The mixture of compounds **3A** and **3B** can be treated with 48% HBr at elevated temperatures, followed by recrystallization or chromatography purifications, to isolate compound **4A** as the minor isomer and compound **4B** as the major isomer. After isolation, compound **4A** can be treated with POCl_3 to provide compound **5**. The formyl group can be converted to an oxime group using NH_2OH to provide compound **6**. The oxime group can be converted to a nitrile group using acetic anhydride to provide compound **7**. The methoxy group of compound **7** can be converted to a hydroxy group by treating compound **7** with aluminum trichloride to provide compound **8**.

[00243] To prepare compound **9**, compound **8** can be reacted with a reagent such as

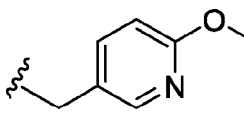


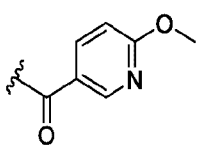
, where X is a leaving atom or group (such as a halide or triflate), in the presence of a suitable base (*e.g.*, a metal alkali carbonate, such as potassium carbonate). Compound **11** can then be prepared by coupling compound **9** with the corresponding boronic ester compound **10**



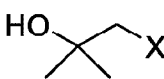
(where Ring D is , wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1 , X^2 , X^3 and X^4 , and the asterisk indicates the point of attachment to P^1 ; X^1 , X^2 , X^3 and X^4 are as defined above; P^1 is an amino protecting group; Z is $-\text{B}(\text{OR}^x)(\text{OR}^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, *e.g.*,

Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $\text{Pd}(\text{PPh}_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures). Compound **12** can then be prepared from compound **11** by removing the protecting group P^1 under standard conditions (for example, a Boc group can be removed by treating compound **11** under acidic conditions, *e.g.*, HCl), followed by functionalization (*i.e.*, reacting or

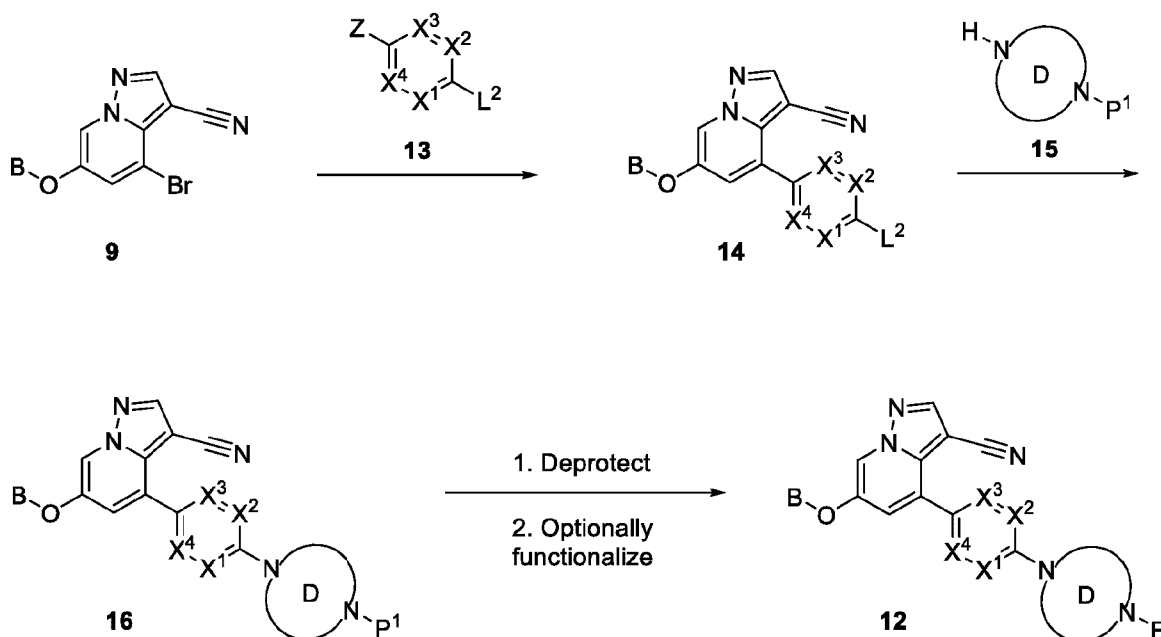
treating compound **11** with the appropriate reagent) to introduce the E group 

(for Formula II) or  (for Formula III) under standard conditions.

[00244] Alternatively, compound **8** can be coupled with the corresponding boronic ester compound **10** to provide compound **11a** using appropriate palladium-catalyzed cross-coupling reaction conditions, *e.g.*, Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $\text{Pd}(\text{PPh}_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures). Compound **11a** can then be reacted with a reagent such as

, where X is a leaving atom or group (such as a halide or triflate), under Mitsunobu reaction conditions (*e.g.*, PPh_3 and diisopropyl azodicarboxylate) to provide compound **11**. Compound **12** can then be prepared from compound **11** as described above.

[00245] Scheme 4



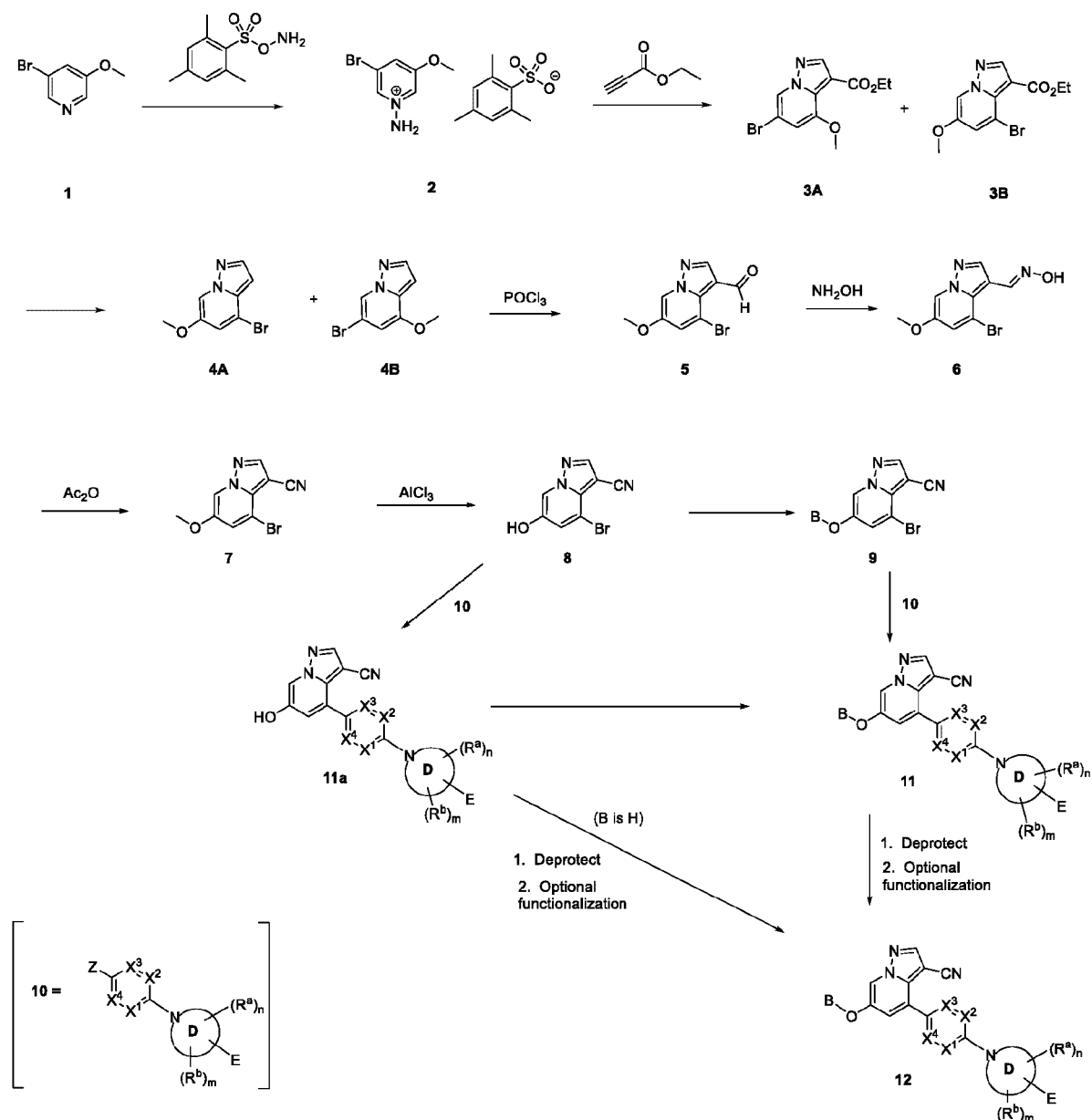
[00246] Scheme 4 shows another general scheme for the synthesis of compound **12** where B, X^1 , X^2 , X^3 , X^4 , Ring D, and E are as defined above for **Scheme 3**.

[00247] Compound **9** (prepared, *e.g.*, as described in **Scheme 3**) in which B is as defined above, can be coupled with the corresponding boronic ester **13** (where X^1 , X^2 , X^3 and X^4 are as defined above; L^2 is a leaving group such as a triflate or halide); Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)), using appropriate palladium-catalyzed cross-coupling reaction conditions, *e.g.*, Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures) to provide compound **14**. Compound **16** can be prepared by coupling compound **14** with compound **15** where Ring D is as defined above and P^1 is an amino protecting group, under appropriate S_NAr conditions (for example, optionally in the presence of a base such as K_2CO_3 and at elevated temperature).

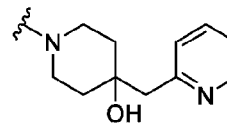
[00248] The protecting group P^1 on Ring D of compound **16** can be removed under standard conditions (for example, a Boc group can be removed by treating compound **16** under acidic conditions, *e.g.*, HCl) to provide compound **12** where E is H (*i.e.*, Ring D is deprotected). The deprotected Ring D can then be functionalized (*i.e.*, reacted or treated with an appropriate reagent)

to introduce the E group under standard conditions such as described below to provide compound **12** where E is as defined above for **Scheme 3**.

[00249] **Scheme 5**



[00250] **Scheme 5** shows a general scheme for the synthesis of the compound of Formula IV (shown as compound **12** for Formula IV in **scheme 5**), where B is $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$; X^1 is N; X^2 ,



X^3 , and X^4 are CH; and D, E, $(R^a)_n$, and $(R^b)_m$ are represented by where the wavy line indicates the point of attachment to the ring comprising X^1 , X^2 , X^3 , and X^4 .

[00251] Compound **2** is obtained by treating 3-bromo-5-methoxypyridine (compound **1**), which is commercially available, with O-(mesitylsulfonyl)hydroxylamine. The O-mesitylsulfonylhydroxylamine may be prepared as described in Mendiola, J., et al., Org. Process Res. Dev. 2009, 13(2), 263-267. Compound **2** may be reacted with ethyl propiolate to provide a mixture of compounds **3A** and **3B**, which typically are obtained in a ratio of approximately 2:1 to 9:1, respectively. The mixture of compounds **3A** and **3B** may be treated with 48% HBr at elevated temperatures, followed by recrystallization or chromatography purifications, to isolate compound **4A** as the minor isomer and compound **4B** as the major isomer. After isolation, compound **4A** may be treated with POCl_3 to provide compound **5**. The formyl group may be converted to an oxime group using NH_2OH to provide compound **6**. The oxime group may be converted to a nitrile group using acetic anhydride to provide compound **7**. The methoxy group of compound **7** may be converted to a hydroxy group by treating compound **7** with aluminum trichloride to provide compound **8**.



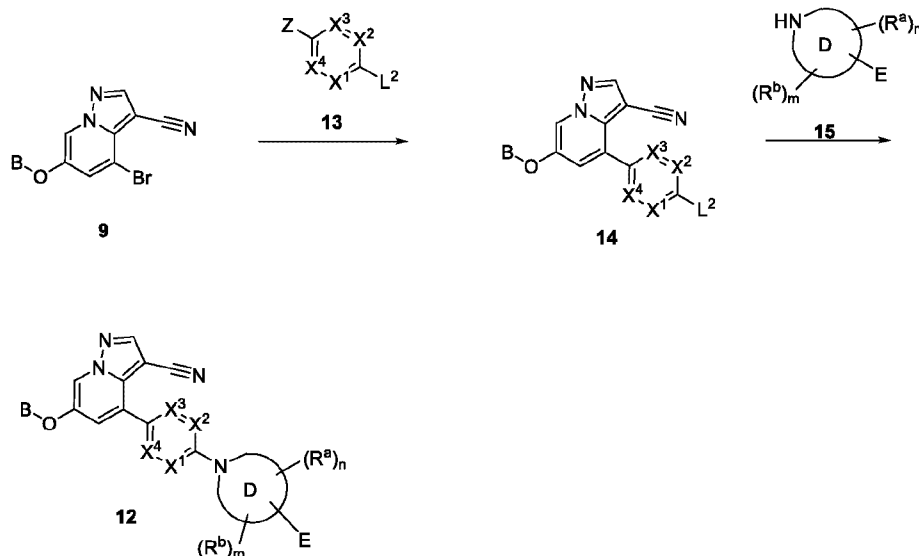
[00252] Compound **11a** may be reacted with a reagent such as a reagent such as where X is a leaving atom or group (such as a halide or triflate), under Mitsunobu reaction conditions (PPh_3 and diisopropyl azodicarboxylate) to provide compound **11**. Compound **12** may then be prepared from compound **11** as described above.

[00253] Alternatively, compound **9** may be prepared by reacting compound **8** with a reagent



such as and X is a leaving atom or group (such as a halide or triflate), in the presence of a base (for example, an alkali metal carbonate, such as potassium carbonate). Compound **11** may then be prepared by coupling compound **9** with the corresponding boronic ester compound **10** using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $\text{Pd}(\text{PPh}_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures).

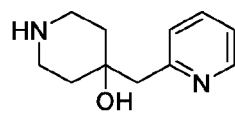
[00254] Scheme 6



[00255] Scheme 6 shows another general scheme for the synthesis of compound **12** where B, X^1 , X^2 , X^3 , X^4 , Ring D and E are as defined above for **Scheme 5**.

[00256] Compound **9** (prepared, e.g., as described in Scheme 5) in which B is as defined for **Scheme 5**, may be coupled with compound **13** (where X^1 , X^2 , X^3 and X^4 are as defined for Scheme 5; L^2 is a leaving group such as a triflate or halide); Z is $-B(OR^x)(OR^y)$ and R^x and R^y are H or (1-6C) alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)), using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures) to provide compound **14**. Compound **12** may be prepared by coupling compound **14** with compound **15** under appropriate S_NAr conditions (for example, optionally in the presence of a base such as K_2CO_3 and at elevated

temperature) where compound 15 is defined as



or salts thereof as described in Formula IV.

[00257] “amino protecting group” as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on the compound. Examples of suitable protecting groups for use in any of the processes described herein include carbamates, amides, alkyl and aryl groups, imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Non-limiting examples of amino protecting groups are acetyl, trifluoroacetyl, t-butyloxycarbonyl (“Boc”), benzyloxycarbonyl (“CBz”) and 9-fluorenylmethylenoxycarbonyl (“Fmoc”). Further examples of these groups, and other protecting groups, are found in T. W. Greene *et al.*, *Greene’s Protective Groups in Organic Synthesis*. New York: Wiley Interscience, 2006.

[00258] Hydroxy groups can be protected with any convenient hydroxy protecting group, for example as described in T. W. Greene *et al.*, *Greene’s Protective Groups in Organic Synthesis*. New York: Wiley Interscience, 2006. Examples include benzyl, trityl, silyl ethers, and the like.

[00259] Nitrogen atoms in compounds described in any of the above methods can be protected with any convenient nitrogen protecting group, for example as described in Greene & Wuts, eds., “Protecting Groups in Organic Synthesis,” 2nd ed. New York; John Wiley & Sons, Inc., 1991. Examples of nitrogen protecting groups include acyl and alkoxycarbonyl groups, such as t-butoxycarbonyl (BOC), phenoxycarbonyl, and [2-(trimethylsilyl)ethoxy]methyl (SEM).

[00260] **3. Methods of treatment**

[00261] The ability of the compound of Formula I-IV, including polymorph forms and pharmaceutically acceptable salts thereof, to act as a RET inhibitor can be demonstrated by the assays described in **Examples 8 and 9**.

[00262] In some embodiments, the compounds provided herein exhibit potent and selective RET inhibition. For example, the compounds provided herein exhibit nanomolar potency against wild type RET and a RET kinase encoded by a RET gene including an activating mutation or a RET kinase inhibitor resistance mutation, including, for example, the KIF5B-RET fusion, G810R and G810S ATP cleft front mutations, M918T activating mutation, and V804M, V804L, and V804E gatekeeper mutations, with minimal activity against related kinases.

[00263] In some embodiments, the compounds provided herein exhibit nanomolar potency against an altered RET fusion protein encoded by a RET gene encoding the RET fusion protein (e.g. any of the RET fusion proteins described herein including, without limitation, CCDC6-RET

or KIF5B-RET) which RET gene includes a RET kinase inhibitor resistance mutation (e.g., any of the RET mutations described herein including, without limitation, V804M, V804L, or V804E) such that the altered RET protein is a RET fusion protein that exhibits RET kinase resistance due to the presence of a RET kinase inhibitor resistance amino acid substitution or deletion. Non-limiting examples include CCDC6-RET-V804M and KIF5B-RET-V804M. In some embodiments, the compounds provided herein exhibit nanomolar potency against an altered RET protein encoded by a RET gene that includes a RET mutation (e.g. any of the RET mutations described herein including, without limitation, C634W or M918T) and that includes a RET kinase inhibitor resistance mutation (e.g., any of the RET kinase inhibitor resistance mutations described herein including, without limitation, V804M, V804L, or V804E) such that the altered RET protein includes a RET substitution caused by the RET mutation (e.g., a RET primary mutation) and the altered RET protein exhibits RET kinase resistance due to the presence of a RET kinase inhibitor resistance amino acid substitution or deletion.

[00264] In some embodiments, the compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, selectively target a RET kinase. For example, a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, can selectively target a RET kinase over another kinase or non-kinase target.

[00265] In some embodiments, a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, exhibits at least a 30-fold selectivity for a RET kinase over another kinase. For example, a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, exhibits at least a 40-fold selectivity; at least a 50-fold selectivity; at least a 60-fold selectivity; at least a 70-fold selectivity; at least a 80-fold selectivity; at least a 90-fold selectivity; at least 100-fold selectivity; at least 200-fold selectivity; at least 300-fold selectivity; at least 400-fold selectivity; at least 500-fold selectivity; at least 600-fold selectivity; at least 700-fold selectivity; at least 800-fold selectivity; at least 900-fold selectivity; or at least 1000-fold selectivity for a RET kinase over another kinase. In some embodiments, selectivity for a RET kinase over another kinase is measured in a cellular assay (e.g., a cellular assay as provided herein).

[00266] In some embodiments, the compounds provided herein can exhibit selectivity for a RET kinase over a KDR kinase (e.g., VEGFR2). In some embodiments, the selectivity for a RET kinase

over a KDR kinase is observed without loss of potency for a RET kinase encoded by a RET gene including an activating mutation or a RET kinase inhibitor resistance mutation (e.g., a gatekeeper mutant). In some embodiments, the selectivity over a KDR kinase is at least 10-fold (e.g., at least a 40-fold selectivity; at least a 50-fold selectivity; at least a 60-fold selectivity; at least a 70-fold selectivity; at least a 80-fold selectivity; at least a 90-fold selectivity; at least 100-fold selectivity; at least 150-fold selectivity; at least 200-fold selectivity; at least 250-fold selectivity; at least 300-fold selectivity; at least 350-fold selectivity; or at least 400-fold selectivity) as compared to the inhibition of KIF5B-RET (e.g., the compounds are more potent against KIF5B-RET than KDR). In some embodiments, the selectivity for a RET kinase over a KDR kinase is about 30-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 100-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 150-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 400-fold. Without being bound by any theory, potent KDR kinase inhibition is believed to be a common feature among multikinase inhibitors (MKIs) that target RET and may be the source of the dose-limiting toxicities observed with such compounds.

[00267] In some embodiments, inhibition of V804M is similar to that observed for wild-type RET. For example, inhibition of V804M is within about 2-fold (e.g., about 5-fold, about 7-fold, about 10-fold) of inhibition of wild-type RET (e.g., the compounds were similarly potent against wild-type RET and V804M). In some embodiments, selectivity for a wildtype or V804M RET kinase over another kinase is measured in an enzyme assay (e.g., an enzyme assay as provided herein). In some embodiments, the compounds provided herein exhibit selective cytotoxicity to RET-mutant cells.

[00268] In some embodiments, inhibition of G810S and/or G810R is similar to that observed for wild-type RET. For example, inhibition of G810S and/or G810R is within about 2-fold (e.g., about 5-fold, about 7-fold, about 10-fold) of inhibition of wild-type RET (e.g., the compounds were similarly potent against wild-type RET and G810S and/or G810R). In some embodiments, selectivity for a wildtype or G810S and/or G810R RET kinase over another kinase is measured in an enzyme assay (e.g., an enzyme assay as provided herein). In some embodiments, the compounds provided herein exhibit selective cytotoxicity to RET-mutant cells.

[00269] In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier

and inhibiting a RET kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a patient with cancer (e.g., a RET-associated cancer such as a RET-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the patient. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, a RET-associated primary brain tumor or metastatic brain tumor.

[00270] In some embodiments, the compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, exhibit one or more of high GI absorption, low clearance, and low potential for drug-drug interactions.

[00271] Compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof are useful for treating diseases and disorders which can be treated with a RET kinase inhibitor, such as RET-associated diseases and disorders, e.g., proliferative disorders such as cancers, including hematological cancers and solid tumors (e.g., advanced solid tumors and/or RET-fusion positive solid tumors), and gastrointestinal disorders such as IBS.

[00272] In certain embodiments, compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof are useful for preventing diseases and disorders as defined herein (for example, autoimmune diseases, inflammatory diseases, and cancer). The term "preventing" as used herein means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

[00273] The term "RET-associated disease or disorder" as used herein refers to diseases or disorders associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a RET gene, a RET kinase, a RET kinase domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of a RET-associated disease or disorder include, for example, cancer and gastrointestinal disorders such as irritable bowel syndrome (IBS).

[00274] The term "RET-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or expression or activity, or level of any of the same. Non-limiting examples of a RET-associated cancer are described herein.

[00275] The phrase “dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a RET kinase domain and a fusion partner, a mutation in a RET gene that results in the expression of a RET protein that includes a deletion of at least one amino acid as compared to a wildtype RET protein, a mutation in a RET gene that results in the expression of a RET protein with one or more point mutations as compared to a wildtype RET protein, a mutation in a RET gene that results in the expression of a RET protein with at least one inserted amino acid as compared to a wildtype RET protein, a gene duplication that results in an increased level of RET protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of RET protein in a cell), an alternative spliced version of a RET mRNA that results in a RET protein having a deletion of at least one amino acid in the RET protein as compared to the wild-type RET protein), or increased expression (e.g., increased levels) of a wildtype RET kinase in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be a mutation in a RET gene that encodes a RET protein that is constitutively active or has increased activity as compared to a protein encoded by a RET gene that does not include the mutation. For example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of RET that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not RET). In some examples, dysregulation of a RET gene, a RET protein, or expression or activity or level of any of the same can be a result of a gene translocation of one RET gene with another non-RET gene. Non-limiting examples of fusion proteins are described in Table 1. Non-limiting examples of RET kinase protein point mutations/insertions/deletions are described in Tables 2 and 2a. Additional examples of RET kinase protein mutations (e.g., point mutations) are RET inhibitor resistance mutations. Non-limiting examples of RET inhibitor resistance mutations are described in Tables 3 and 4.

[00276] In some embodiments, dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same can be caused by an activating mutation in a RET gene (see, e.g., chromosome translocations that result in the expression of any of the fusion proteins listed in

Table 1). In some embodiments, dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same can be caused by a genetic mutation that results in the expression of a RET kinase that has increased resistance to inhibition by a RET kinase inhibitor and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wildtype RET kinase (see, e.g., the amino acid substitutions in Tables 3 and 4). In some embodiments, dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same can be caused by a mutation in a nucleic acid encoding an altered RET protein (e.g., a RET fusion protein or a RET protein having a mutation (e.g., a primary mutation)) that results in the expression of an altered RET protein that has increased resistance to inhibition by a RET kinase inhibitor and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wildtype RET kinase (see, e.g., the amino acid substitutions in Tables 3 and 4). The exemplary RET kinase point mutations, insertions, and deletions shown in Tables 2 and 2a can be caused by an activating mutation and/or can result in the expression of a RET kinase that has increased resistance to inhibition by a RET kinase inhibitor and/or a multi-kinase inhibitor (MKI).

[00277] The term “activating mutation” describes a mutation in a RET kinase gene that results in the expression of a RET kinase that has an increased kinase activity, e.g., as compared to a wildtype RET kinase, e.g., when assayed under identical conditions. For example, an activating mutation can result in the expression of a fusion protein that includes a RET kinase domain and a fusion partner. In another example, an activating mutation can be a mutation in a RET kinase gene that results in the expression of a RET kinase that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acid substitutions (e.g., any combination of any of the amino acid substitutions described herein) that has increased kinase activity, e.g., as compared to a wildtype RET kinase, e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in a RET kinase gene that results in the expression of a RET kinase that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acids deleted, e.g., as compared to a wildtype RET kinase, e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in a RET kinase gene that results in the expression of a RET kinase that has at least one (e.g., at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 14, at least 16, at least 18, or at least 20) amino acid inserted as compared to a wildtype RET kinase, e.g., the exemplary wildtype RET kinase described herein, e.g., when assayed under identical conditions. Additional

examples of activating mutations are known in the art.

[00278] The term "wildtype" or "wild-type" describes a nucleic acid (e.g., a RET gene or a RET mRNA) or protein (e.g., a RET protein) that is found in a subject that does not have a RET-associated disease, e.g., a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease), or is found in a cell or tissue from a subject that does not have a RET-associated disease, e.g., a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease).

[00279] The term "regulatory agency" refers to a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[00280] Provided herein is a method of treating cancer (e.g., a RET-associated cancer) in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof. For example, provided herein are methods for treating a RET-associated cancer in a patient in need of such treatment, the method comprising a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more fusion proteins. Non-limiting examples of RET gene fusion proteins are described in Table 1. In some embodiments, the fusion protein is KIF5B-RET. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET kinase protein point mutations/insertions. Non-limiting examples of RET kinase protein point mutations/insertions/deletions are described in Tables 2 and 2a. In some embodiments, the RET kinase protein point mutations/insertions/deletions are selected from the group consisting of M918T, M918V, C634W, V804L, V804M, G810S, and G810R. In some embodiments, the RET kinase protein point mutations/insertions/deletions occur in a RET fusion protein (e.g., any of the RET gene fusion proteins described in Table 1). In some embodiments, a compound of Formula I-IV is a polymorph

form. In some embodiments, the compound is polymorph Form A of the compound of Formula I. In some embodiments, the compound is polymorph Form 1 of the compound of Formula II. In some embodiments, the compound is polymorph Form 2 of the compound of Formula II. In some embodiments, the compound is polymorph Form 7 of the compound of Formula II. In some embodiments, the compound is polymorph Form 8 of the compound of Formula II. In some embodiments, the compound is polymorph Form A of the compound of Formula III. In some embodiments, the compound is polymorph Form A of the compound of Formula IV. In some embodiments, the compound is polymorph Form B of the compound of Formula IV.

[00281] In some embodiments, the compound of Formula I-IV is a pharmaceutically acceptable salt. In some embodiments, the compound is a chloride salt of the compound of Formula I. In some embodiments, the compound is a bromide salt of the compound of Formula I. In some embodiments, the compound is an L-malate salt of the compound of Formula I. In some embodiments, the compound is a D-malate salt of the compound of Formula I. In some embodiments, the compound is a phosphate salt of the compound of Formula II. In some embodiments, the phosphate salt is a sesqui-phosphate salt (*e.g.*, 1.4:1, PO₄:free base).

[00282] In some embodiments of any of the methods or uses described herein, the cancer (*e.g.*, RET-associated cancer) is a hematological cancer. In some embodiments of any of the methods or uses described herein, the cancer (*e.g.*, RET-associated cancer) is a solid tumor (*e.g.*, an advanced solid tumor and/or a RET-fusion positive solid tumor). In some embodiments of any of the methods or uses described herein, the cancer (*e.g.*, RET-associated cancer) is a lung cancer (*e.g.*, small cell lung carcinoma or non-small cell lung carcinoma), thyroid cancer (*e.g.*, papillary thyroid cancer, medullary thyroid cancer (*e.g.*, sporadic medullary thyroid cancer or hereditary medullary thyroid cancer), differentiated thyroid cancer, recurrent thyroid cancer, or refractory differentiated thyroid cancer), thyroid adenoma, endocrine gland neoplasms, lung adenocarcinoma, bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, mammary cancer, mammary carcinoma, mammary neoplasm, colorectal cancer (*e.g.*, metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastrointestinal mucosa, inflammatory myofibroblastic tumor, or cervical cancer. In some embodiments of any of the methods or uses described herein, the cancer (*e.g.*, RET-associated cancer) is selected from the group of: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), cancer in

adolescents, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, unknown primary carcinoma, cardiac tumors, cervical cancer, childhood cancers, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasms, neoplasms by site, neoplasms, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, cutaneous angiosarcoma, bile duct cancer, ductal carcinoma in situ, embryonal tumors, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic disease, glioma, hairy cell tumor, hairy cell leukemia, head and neck cancer, thoracic neoplasms, head and neck neoplasms, CNS tumor, primary CNS tumor, heart cancer, hepatocellular cancer, histiocytosis, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone, osteocarcinoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, neoplasms by site, neoplasms, myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative neoplasms, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, lung neoplasm, pulmonary cancer, pulmonary neoplasms, respiratory tract neoplasms, bronchogenic carcinoma, bronchial neoplasms, oral cancer, oral cavity cancer, lip cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromosytoma, pituitary cancer, plasma cell neoplasm, pleuropulmonary blastoma, pregnancy-associated breast cancer, primary central nervous system lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, colon cancer, colonic neoplasms, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome,

skin cancer, Spitz tumors, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, unknown primary carcinoma, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

[00283] In some embodiments, a hematological cancer (e.g., hematological cancers that are RET-associated cancers) is selected from the group consisting of leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM). Additional examples of hematological cancers include myeloproliferative disorders (MPD) such as polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). In one embodiment, the hematological cancer (e.g., the hematological cancer that is a RET-associated cancer) is AML or CMML.

[00284] In some embodiments, the cancer (e.g., the RET-associated cancer) is a solid tumor. Examples of solid tumors (e.g., solid tumors that are RET-associated cancers) include, for example, thyroid cancer (e.g., papillary thyroid carcinoma, medullary thyroid carcinoma), lung cancer (e.g., lung adenocarcinoma, small-cell lung carcinoma), pancreatic cancer, pancreatic ductal carcinoma, breast cancer, colon cancer, colorectal cancer, prostate cancer, renal cell carcinoma, head and neck tumors, neuroblastoma, and melanoma. See, for example, *Nature Reviews Cancer*, 2014, 14, 173-186.

[00285] In some embodiments, the cancer is selected from the group consisting of lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa,

and cervical cancer.

[00286] In some embodiments, the patient is a human.

[00287] Compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof are also useful for treating a RET-associated cancer.

[00288] Accordingly, also provided herein is a method for treating a patient diagnosed with or identified as having a RET-associated cancer, e.g., any of the exemplary RET-associated cancers disclosed herein, comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition thereof as defined herein.

[00289] Dysregulation of a RET kinase, a RET gene, or the expression or activity or level of any (e.g., one or more) of the same can contribute to tumorigenesis. For example, a dysregulation of a RET kinase, a RET gene, or expression or activity or level of any of the same can be a translocation, overexpression, activation, amplification, or mutation of a RET kinase, a RET gene, or a RET kinase domain. Translocation can include a gene translocation resulting in the expression of a fusion protein that includes a RET kinase domain and a fusion partner. For example, a fusion protein can have increased kinase activity as compared to a wildtype RET protein. In some embodiments, a mutation in a RET gene can involve mutations in the RET ligand-binding site, extracellular domains, kinase domain, and in regions involved in protein:protein interactions and downstream signaling. In some embodiments, a mutation (e.g., an activating mutation) in a RET gene can result in the expression of a RET kinase having one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acid substitutions (e.g., one or more amino acid substitutions in the kinase domain (e.g., amino acid positions 723 to 1012 in a wildtype RET protein), a gatekeeper amino acid (e.g., amino acid position 804 in a wildtype RET protein), the P-loop (e.g., amino acid positions 730-737 in a wildtype RET protein), the DFG motif (e.g., amino acid positions 892-894 in a wildtype RET protein), ATP cleft solvent front amino acids (e.g., amino acid positions 758, 811, and 892 in a wildtype RET protein), the activation loop (e.g., amino acid positions 891-916 in a wildtype RET protein), the C-helix and loop preceeding the C-helix (e.g., amino acid positions 768-788 in a wildtype RET protein), and/or the ATP binding site (e.g., amino acid positions 730-733, 738, 756, 758, 804, 805, 807, 811, 881, and 892 in a wildtype RET protein). In some embodiments, a mutation can be a gene amplification of a RET gene. In some embodiments, a mutation (e.g., an activating mutation) in a RET gene can result in the expression

of a RET kinase or RET receptor that lacks at least one amino acid (e.g., at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 14, at least 16, at least 18, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, or at least 50 amino acids) as compared to a wildtype RET protein. In some embodiments, dysregulation of a RET kinase can be increased expression (e.g., increased levels) of a wildtype RET kinase in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). In some embodiments, a mutation (e.g., an activating mutation) in a RET gene can result in the expression of a RET kinase or RET receptor that has at least one amino acid (e.g., at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 14, at least 16, at least 18, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, or at least 50 amino acids) inserted as compared to a wildtype RET protein. In some embodiments, dysregulation of a RET kinase can be increased expression (e.g., increased levels) of a wildtype RET kinase in a mammalian cell (e.g., as compared to a control non-cancerous cell), e.g., due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling. Other dysregulations can include RET mRNA splice variants. In some embodiments, the wildtype RET protein is the exemplary wildtype RET protein described herein.

[00290] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes overexpression of wild-type RET kinase (e.g., leading to autocrine activation). In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, includes overexpression, activation, amplification, or mutation in a chromosomal segment comprising the RET gene or a portion thereof, including, for example, the kinase domain portion, or a portion capable of exhibiting kinase activity.

[00291] In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in a RET gene fusion. In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-RET partner protein, and includes a minimum of a functional RET kinase domain.

[00292] Non-limiting examples of RET fusion proteins are shown in **Table 1**.

Table 1. Exemplary RET Fusion Partners and Cancers

Fusion Partner	Non-limiting Exemplary RET- Associated Cancer(s)
BCR	Chronic Myelomonocytic Leukemia (CMML)
CLIP1	Adenocarcinoma
KIF5B	NSCLC, Ovarian Cancer, Spitzoid Neoplasms; Lung Adenocarcinoma ^{3, 4, 14, 28,} Adenosquamous Carcinomas ¹⁵
CCDC6 (also called PTC1, D10S170, or H4)	NSCLC, Colon Cancer, Papillary Thyroid Cancer; Adenocarcinomas; Lung Adenocarcinoma; Metastatic Colorectal Cancer ⁵ ; Adenosquamous Carcinomas ¹⁵ , Breast Cancer ³⁰
PTC1ex9 (a novel CCDC6 rearrangement)	Metastatic papillary thyroid cancer ²
NCOA4 (also called PTC3, ELE1, and RFG)	Papillary Thyroid Cancer ²¹ , NSCLC, Colon Cancer, Salivary Gland Cancer, Metastatic Colorectal Cancer ⁵ ; Lung Adenocarcinoma ¹⁵ ; Adenosquamous Carcinomas ¹⁵ Diffuse

Fusion Partner	Non-limiting Exemplary RET- Associated Cancer(s)
	Sclerosing Variant of Papillary Thyroid Cancer ¹⁶ , Breast Cancer ³⁰ , Acinic Cell Carcinoma ³² , Mammary Analog Secretory Carcinoma ³³
TRIM33 (also called PTC7, RFG7, and TIF1G)	NSCLC, Papillary Thyroid Cancer, Lung Adenocarcinoma ⁴⁶ , Various ²²
ERC1 (also called ELKS and RAB61P2)	Papillary Thyroid Cancer, Breast Cancer
FGFR1OP	CMML, Primary Myelofibrosis with secondary Acute Myeloid Leukemia
MBD1(also known as PCM1)	Papillary Thyroid Cancer
PRKAR1A (also called PTC2)	Papillary Thyroid Cancer
TRIM24 (also called PTC6)	Papillary Thyroid Cancer
KTN1 (also called PTC8)	Papillary Thyroid Cancer
GOLGA5 (also called PTC5)	Papillary Thyroid Cancer, Spitzoid Neoplasms
HOOK3	Papillary Thyroid Cancer

Fusion Partner	Non-limiting Exemplary RET- Associated Cancer(s)
KIAA1468 (also called PTC9 and RFG9)	Papillary Thyroid Cancer, Lung Adenocarcinoma ^{8, 12}
TRIM27 (also called RFP)	Papillary Thyroid Cancer
AKAP13	Papillary Thyroid Cancer
FKBP15	Papillary Thyroid Cancer, Acute Myeloid Leukemia ⁴⁶
SPECC1L	Papillary Thyroid Cancer; Thyroid Gland Carcinoma
TBL1XR1	Papillary Thyroid Cancer; Thyroid Gland Carcinoma
CEP55	Diffuse Gastric Cancer ⁷
CUX1	Lung Adenocarcinoma
ACBD5	Papillary Thyroid Carcinoma
MYH13	Medullary Thyroid Carcinoma ¹
Uncharacterized	Inflammatory Myofibroblastic Tumor ⁶
PIBF1	Bronchiolus Lung Cell Carcinoma ⁹
KIAA1217 (also called SKT)	Papillary Thyroid Cancer ^{10, 13} Lung Adenocarcinoma ¹⁴ NSCLC ¹⁴
MPRIP	NSCLC ¹¹

Fusion Partner	Non-limiting Exemplary RET- Associated Cancer(s)
HRH4-RET	Thyroid Cancer and/or Paillary Thyroid Carcinoma ¹⁷
Ria-RET	Thyroid Cancer and/or Papillary Thyroid Carcinoma ¹⁷
RFG8	Papillary Thyroid Carcinoma ¹⁸
FOXP4	Lung Adenocarcinoma ¹⁹
MYH10	Infantile Myofibromatosis ²⁰
HTIF1	Various ²²
H4L	Various ²²
PTC4 (a novel NCO4/ELE1 rearrangement)	Papillary Thyroid Cancer ²³
FRMD4A	NSCLC ²⁴
SQSTM1	Papillary Thyroid Carcinoma ²⁵
AFAP1L2	Papillary Thyroid Carcinoma ²⁵
AFAP1	NSCLC ³¹
PPFIBP2	Papillary Thyroid Carcinoma ²⁵
EML4	NSCLC
PARD3	NSCLC ²⁷
RASGEF1A	Breast Cancer ³⁰

Fusion Partner	Non-limiting Exemplary RET- Associated Cancer(s)
TEL (also called ETV6)	<i>In vitro</i> ³⁴ , secretory carcinoma ⁵¹
RUFY1	Colorectal Cancer ³⁵
OLFM4	Small-Bowel Cancer ³⁶
UEVLD	Papillary Thyroid Carcinoma ²⁹
DLG5	Non-Anaplastic Thyroid (NAT) Cancer ³⁷
RRBP1	Colon Cancer ³⁸
ANK3	Papillary Thyroid Carcinoma ³⁹
PICALM	NSCLC ⁴⁰
MYO5C	NSCLC ⁴¹
EPHA5	NSCLC ⁴⁰
RUFY2	Lung Cancer ⁴²
KIF13A	Lung Adenocarcinoma ⁴³ , NSCLC ⁴⁵
TNIP1	Colorectal Cancer ⁴⁴
SNRNP70	Colorectal Cancer ⁴⁴
MRLN	Thyroid Carcinoma ⁴⁶
LMNA	Spitzoid Melanoma ⁴⁷
RUFY3	Papillary Thyroid Carcinoma
TFG	
MYO5A	Pigmented spindle cell nevus (PSCN) of Reed ⁴⁸
ADD3	Lung adenocarcinoma ⁴⁹

Fusion Partner	Non-limiting Exemplary RET- Associated Cancer(s)
JMJD1C	NSCLC ⁵⁰
RBPM5	
DOCK1	
TAF3	
NCOA1	NSCLC ⁵²

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² Halkova et al., *Human Pathology* 46:1962-1969, 2015.

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⁴ U.S. Patent No. 9,216,172

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⁷ U.S. Patent Application Publication No. 2015/0177246.

⁸ U.S. Patent Application Publication No. 2015/0057335.

⁹ Japanese Patent Application Publication No. 2015/109806A.

¹⁰ Chinese Patent Application Publication No. 105255927A.

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¹² European Patent Application Publication No. EP3037547A1.

¹³ Lee et al., *Oncotarget*. DOI: 10.18632/oncotarget.9137, e-published ahead of printing, 2016.

¹⁴ Saito et al., *Cancer Science* 107:713-720, 2016.

¹⁵ Pirker et al., *Transl. Lung Cancer Res.* 4(6):797-800, 2015.

¹⁶ Joung et al., *Histopathology* 69(1):45-53, 2016.

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¹⁹ Bastien et al., *Journal of Molecular Diagnostics*, 18(6):1027, Abstract Number: S120, 2016

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- ²⁸ U.S. Patent Application Publication No. 2017/0014413.
- ²⁹ Lu et al., *Oncotarget*, 8(28):45784-45792, doi: 10.18632/oncotarget.17412, 2017.
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[00293] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes one or more deletions (e.g., deletion of an amino acid at position 4), insertions, or point mutation(s) in a RET kinase. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes a deletion of one or more residues from the RET kinase, resulting in constitutive activity of the RET kinase domain.

[00294] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions, insertions,

or deletions as compared to the wild-type RET kinase (see, for example, the point mutations listed in **Table 2**).

Table 2. RET Kinase Protein Amino Acid Substitutions/Insertions/ Deletions^A

Amino acid position 2
Amino acid position 3
Amino acid position 4
Amino acid position 5
Amino acid position 6
Amino acid position 7
Amino acid position 8
Amino acid position 11
Amino acid position 12
Amino acid position 13
Amino acid position 20
Amino acid position 32 (e.g., S32L)
Amino acid position 34 (e.g., D34S)
Amino acid position 40 (e.g., L40P)
Amino acid position 45 (e.g., A45A) ³⁹
Amino acid position 56 (e.g., L56M) ³⁰
Amino acid position 64 (e.g., P64L)
Amino acid position 67 (e.g., R67H)
Amino acid position 77 (e.g., R77C) ⁶⁵
Amino acid position 114 (e.g., R114H)
Amino acid position 136 (e.g., glutamic acid to stop codon)
Amino acid position 145 (e.g., V145G)
Amino acid position 177 (e.g., R177L) ⁶⁷
Amino acid position 180 (e.g., arginine to stop codon)
Amino acid position 200

Amino acid position 270 (e.g., P270L) ⁶⁵
Amino acid position 278 (e.g., T278N) ⁵⁷
Amino acid position 292 (e.g., V292M)
Amino acid position 294
Amino acid position 321 (e.g., G321R)
Amino acid position 330 (e.g., R330Q)
Amino acid position 338 (e.g., T338I)
Amino acid position 360 (e.g., R360W)
Amino acid position 373 (e.g., alanine to frameshift)
Δ Amino acid positions 378 – 385 with insertion of one amino acid (e.g., D378 – G385>E)
Amino acid position 393 (e.g., F393L)
Amino acid position 423 (e.g., G423R) ²⁷
Amino acid position 428 (e.g., E428K) ⁵⁷
Amino acid position 432 (e.g., A432A ³⁹)
Amino acid position 446 (e.g., G446R) ²⁸
Δ Amino acid positions 505-506 (6-Base Pair In-Frame Germline Deletion in Exon 7) ³
Amino acid position 510 (e.g., A510V)
Amino acid position 511 (e.g., E511K)
Amino acid position 513 (e.g., G513D) ^{7*}
Amino acid position 515 (e.g., C515S, C515W ⁴)
Amino acid position 525 (e.g., R525W) ^{7*}
Amino acid position 531 (e.g., C531R, or 9 base pair duplication ²)
Amino acid position 532 (e.g., duplication) ²
Amino acid position 533 (e.g., G533C, G533S)
Amino acid position 534 (e.g., L534L) ⁶
Amino acid position 550 (e.g., G550E)
Amino acid position 591 (e.g., V591I)

Amino acid position 593 (e.g., G593E)
Amino acid position 595 (e.g., E595D and E595A) ¹⁸
Amino acid position 600 (e.g., R600Q)
Amino acid position 602 (e.g., I602V) ⁶
Amino acid position 603 (e.g., K603Q, K603E ²)
Amino acid position 606 (e.g., Y606C)
Amino acid position 609 (e.g., C609Y, C609S, C609G, C609R, C609F, C609W, C609C ³²)
Amino acid position 611 (e.g., C611R, C611S, C611G, C611Y, C611F, C611W)
Amino acid position 616 (e.g., E616Q) ²³
Δ Amino acid position 616 ⁶⁴
Amino acid position 618 (e.g., C618S, C618Y, C618R, C618G, C618F, C618W, stop ⁵⁶)
Amino acid position 619 (e.g., F619F)
Amino acid position 620 (e.g., C620S, C620W, C620R, C620G, C620L, C620Y, C620F, C620A ⁴⁷)
Δ Amino acid positions 612-620 ⁷⁴
Amino acid position 622 (e.g., P622L) ⁶⁸
Amino acid position 623 (e.g., E623K)
Amino acid position 624 (e.g., D624N)
Amino acid position 628 (e.g., P628N) ⁷³
Amino acid positions 629-631 (e.g., L629-D631delinsH) ⁸⁰
Amino acid position 630 (e.g., C630A, C630R, C630S, C630Y, C630F, C630W)
Δ Amino acid position 630 ⁵⁶
Amino acid position 631 (e.g., D631N, D631Y, D631A, D631G, D631V, D631E,)
Δ Amino acid position 631 ⁶⁹

Amino acid positions 631-633>V (i.e., residues 631-633 are replaced with a single valine residue)
Amino acid positions 631-633>A (i.e., residues 631-633 are replaced with a single alanine residue)
Amino acid positions 631-633>E (i.e., residues 631-633 are replaced with a single glutamic acid residue)
Δ Amino acid positions 631-633 (e.g., D631 – L633)
Δ Amino acid positions 631-634 (e.g., D631-C634)
Amino acid position 632 (e.g., E632K, E632G ^{5, 11} , E632V ⁶² , 632 to frameshift ⁴⁷)
Amino acid positions 632-633>V (i.e., residues 632 and 633 are replaced with a single valine residue) ⁷⁴
Δ Amino acid positions 632-633 (e.g., E632 – L633 in either the somatic cells, or a 6-Base Pair In-Frame Germline Deletion in Exon 11 ⁹)
Amino acid positions 632-639>HR (i.e., residues 632-639 are replaced with two residues, histidine and arginine)
Amino acid position 633 (e.g., L633R ⁶² , 9 base pair duplication ² , L633delinsLCR ⁷¹)
Amino acid position 634 (e.g., C634W, C634Y, C634S, C634R, C634F, C634G, C634L, C634A, or C634T, a 9 base pair deletion ⁶² , a 9 base pair duplication ⁵⁶ , or a 12 base pair duplication ²) (e.g., causing MTC)
Δ Amino acid position 634 ⁵⁶
Amino acid position 632/633/634 (E632V/L633R/634 9 base pair deletion) ⁶²
Amino acid position 635 (e.g., R635G or an insertion ELCR ²)

Amino acid position 636 (e.g., T636P ² , T636M ⁴)
Amino acid positions 636-637 (e.g., T636-V637insCRT) ⁸⁰
Amino acid position 638 (e.g., isoleucine to frameshift ⁴⁷)
Amino acid position 640 (e.g., A640G)
Amino acid position 634/640 (e.g., C634R/A640G) ⁵⁶
Amino acid position 641 (e.g., A641S, A641T ⁸)
Amino acid position 634/641 (e.g., C634S/A641S) ⁵⁶
Amino acid position 639/641 (e.g., A639G/A641R) ⁵⁶
Amino acid position 644 (e.g., T644M) ⁵⁹
Amino acid position 648 (e.g., V648I)
Amino acid positions 634/648 (e.g., C634R/V648I) ⁷⁷
Amino acid position 649 (e.g., S649L) ²⁸
Amino acid position 661 (e.g., H661H) ⁶
Amino acid position 664 (e.g., A664D)
Amino acid position 665 (e.g., H665Q)
Amino acid position 666 (e.g., K666E, K666M, K666N, K666R)
Amino acid position 675 (T675T, silent nucleotide change) ¹⁸
Amino acid position 679 (e.g., P679P) ⁶
Amino acid position 680 (e.g., A680T, alanine to frameshift) ⁶
Amino acid position 686 (e.g., S686N)
Amino acid position 689 (e.g., S689T) ¹⁸
Amino acid position 691 (e.g., G691S)
Amino acid position 694 (e.g., R694Q)
Amino acid position 700 (e.g., M700L)
Amino acid position 706 (e.g., V706M, V706A)

Amino acid position 713 splice variant (e.g., E713K (e.g., a splice variant))) ⁶
Amino acid position 714 (e.g., D714Y) ⁵⁷
Amino acid position 727 (e.g., G727E) ⁶
Amino acid position 732 (e.g., E732K) ²⁰
Amino acid position 734 (e.g., E734K) ⁴⁸
Amino acid position 736 (e.g., G736R) ⁶
Amino acid position 738 (e.g., V738V) ⁶
Amino acid position 742 (e.g., T742M) ⁵¹
Amino acid position 748 (e.g., G748C)
Amino acid position 749 (e.g., R749T) ³⁶
Amino acid position 750 (e.g., A750P, A750G) ⁶
Amino acid position 752 (e.g., Y752Y) ⁶
Amino acid position 751 (e.g., G751G) ⁶
Amino acid position 762 (e.g., E762Q) ³⁶
Amino acid position 765 (e.g., S765P, S765F)
Amino acid position 766 (e.g., P766S, P766M) ⁶
Amino acid position 768 (e.g., E768Q, E768D, E768N ⁴⁶ , E768G ⁷²)
Amino acid position 769 (e.g., L769L) ⁶
Amino acid position 770 (e.g., R770Q)
Amino acid position 771 (e.g., D771N)
Amino acid position 777 (e.g., N777S)
Amino acid position 778 (e.g., V778I)
Amino acid position 781 (e.g., Q781R)
Amino acid position 788 (e.g., I788I ³² , I788N ⁷⁸)
Amino acid position 790 (e.g., L790F)
Amino acid position 768/790 (e.g., E768D/L790T) ⁴⁰
Amino acid position 791 (e.g., Y791F, Y791N ²⁴)

Amino acid position 634/791 (e.g., C634Y/Y791F) ⁵⁵
Amino acid position 790/791 (e.g., L790F/Y791F) ⁵⁵
Amino acid position 802
Amino acid position 804 (e.g., V804L ^{15, 16} , V804M ^{15, 16} , V804E ¹²) (e.g., causing MTC)
Amino acid position 778/804 ⁵⁰ (e.g., V778I/V804M ⁵⁴)
Amino acid position 781/804 (e.g., Q781R/V804M) ⁴¹
Amino acid position 805 (e.g., E805K)
Amino acid position 804/805 (e.g., V804M/E805K) ¹⁷
Amino acid position 806 (e.g., Y806F, Y806S ¹² , Y806G, Y806C ^{2, 12, 14} , Y806E ¹⁴ , Y806H ¹² , Y806N ¹² , Y806Y ³²)
Amino acid position 804/806 (e.g., V804M/Y806C) ³⁸
Amino acid position 810 (e.g., G810R ¹² , G810S ¹² , G810A ¹³ , G810C, G810V, and G810D)
Amino acid position 818 (e.g., E818K)
Amino acid position 819 (e.g., S819I)
Amino acid position 820 (e.g., R820L) ⁵⁷
Amino acid position 823 (e.g., G823E)
Amino acid position 826 (e.g., Y826M, Y826S) ¹⁰
Amino acid position 828 (e.g., G828R) ⁵⁷
Amino acid position 833 (e.g., R833C)
Amino acid position 836 (e.g., S836S) ¹⁹
Amino acid position 841 (e.g., P841L, P841P)
Amino acid position 843 (e.g., E843D)
Amino acid position 844 (e.g., R844W, R844Q, R844L)
Amino acid position 804/844 (e.g., V804M/R844L) ⁷⁶
Amino acid position 845 (e.g., A845A) ⁶³
Amino acid position 848 (e.g., M848T)

Amino acid position 852 (e.g., I852M)
Amino acid position 853 (e.g., S853T) ⁵⁷
Amino acid position 865 (e.g., L865V) ¹²
Amino acid position 866 (e.g., A866W) ³³
Amino acid position 867 (e.g., E867K) ³⁷
Amino acid position 870 (e.g., L870F) ¹²
Amino acid position 873 (e.g., R873W, R873Q ⁴²)
Amino acid position 876 (e.g., A876V)
Amino acid position 881 (e.g., L881V)
Amino acid position 882
Amino acid position 883 (e.g., A883F, A883S, A883T, A883Y ⁵³ , A883V)
Amino acid position 884 (e.g., E884K, E884V ³⁵)
Amino acid position 886 (e.g., R886W)
Amino acid position 891 (e.g., S891A, S891S ³² , S891L ³⁵)
Amino acid position 893 (e.g., F893L) ⁴²
Amino acid position 894 (e.g., G894S) ⁴³
Amino acid position 897 (e.g., R897Q, R897P)
Amino acid position 898 (e.g., D898V, D898Y ⁶⁶)
Δ Amino acid position 898
Δ Amino acid positions 898-902 ⁵⁸
Δ Amino acid positions 899-902 ⁴⁷
Δ Amino acid positions 898-901 ⁴⁷
Δ Amino acid positions 632-633/Δ Amino acid positions 898-901 ⁴⁷
Amino acid position 900 (e.g., Y900F) ²²
Amino acid position 901 (e.g., E901K)
Amino acid position 904 (e.g., S904F, S904S, S904C ² , S904T ⁵⁷)

Amino acid position 691/904 (e.g., G691S/S904S) ⁴⁹
Amino acid position 804/904 (e.g., V804M/S904C) ³⁸
Amino acid position 905 (e.g., Y905F) ²²
Amino acid position 907 (e.g., K907E, K907M)
Amino acid position 908 (e.g., R908K)
Amino acid position 911 (e.g., G911D, G911G (e.g., a splice variant) ⁶)
Amino acid position 912 (e.g., R912P, R912Q)
Amino acid position 918 (e.g., M918T ² , M918V, M918L ⁶) (e.g., causing MTC)
Amino acid position 591/918 (e.g., V591I/M918T) ⁶¹
Amino acid position 620/918 (e.g., C620F/M918T) ⁴⁷
Amino acid position 891/918 (e.g., S891A/M918T) ⁴⁷
Δ Amino acid position 898-901/M918T ⁴⁷
Amino acid position 919 (e.g., A919V, A919P ⁵²)
Amino acid position 768/919 ⁵⁴
Amino acid position 921 (e.g., E921K, E921D)
Amino acid position 911/918/921 (e.g., G911E/M918T/E921K) ⁶¹
Amino acid position 922 (e.g., S922P, S922Y)
Amino acid position 924 (e.g., F924S) ⁶
Amino acid position 930 (e.g., T930M)
Amino acid position 961 (e.g., F961L)
Amino acid position 972 (e.g., R972G)
Amino acid position 973 (e.g., P973T) ⁵⁷
Amino acid position 977 (e.g., S977R) ³⁷
Amino acid position 981 (e.g., Y981F) ²²
Amino acid position 982 (e.g., R982C) ⁷⁰

Amino acid position 634/691/982 (e.g., C634R/G691S/R982C) ⁴⁵
Amino acid position 292/67/982 (e.g., V292M/R67H/R982C) ⁷⁵
Amino acid position 634/292/67/982 (e.g., C634R/V292M/R67H/R982C) ⁷⁵
Amino acid position 1009 (e.g., M1009V)
Amino acid position 1015 (e.g., Y1015F) ²²
Amino acid position 1017 (e.g., D1017N)
Amino acid position 1024 (e.g., S1024F) ⁷⁹
Amino acid position 1041 (e.g., V1041G)
Amino acid position 1047 (e.g., P1047S) ⁶⁵
Amino acid position 1051 (e.g., A1051T) ⁵⁷
Δ Amino acid position 1059 ⁵⁷
Amino acid position 1064 (e.g., M1064T)
Amino acid position 1096 (e.g., Y1096F) ²¹
Amino acid position 1105 (e.g., A1105V) ⁵⁷
Amino acid position 1109 (e.g., M1109T) ³⁴
RET+3 ¹
(In-Frame Deletion in Exons 6 and 11) ²⁵
(3bp In-Frame Deletion in Exon 15) ²⁶
Nucleotide position 2136+2 (e.g., 2136+2T>G) ²⁹
(del632-636 ins6) ³¹
Amino acid positions 791 and 852 (e.g., Y791F + I852M) ³¹
Amino acid positions 634 and 852 (e.g., C634R + I852M) ³¹
c.1893_1895del ⁴⁴

^A The RET kinase mutations shown may be activating mutations and/or confer increased resistance of the RET kinase to a RET kinase inhibitor and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wildtype RET kinase.

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[00295] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type RET kinase (see, for example, the point mutations listed in **Table 2a**).

[00296] **Table 2a RET Kinase Protein Amino Acid Substitutions/Insertions/Deletions^A**

Amino acid position 20
Amino acid position 32 (e.g., S32L)
Amino acid position 34 (e.g., D34S)
Amino acid position 40 (e.g., L40P)
Amino acid position 64 (e.g., P64L)
Amino acid position 67 (e.g., R67H)
Amino acid position 114 (e.g., R114H)
Amino acid position 145 (e.g., V145G)
Amino acid position 200
Amino acid position 292 (e.g., V292M)
Amino acid position 294

Amino acid position 321 (e.g., G321R)
Amino acid position 330 (e.g., R330Q)
Amino acid position 338 (e.g., T338I)
Amino acid position 360 (e.g., R360W)
Amino acid position 393 (e.g., F393L)
Amino acid position 432
Δ Amino acid residues 505-506 (6-Base Pair In-Frame Germline Deletion in Exon 7)
Amino acid position 510 (e.g., A510V)
Amino acid position 511 (e.g., E511K)
Amino acid position 513 (e.g., G513D)
Amino acid position 515 (e.g., C515S, C515W ⁴)
Amino acid position 525 (e.g., R525W)
Amino acid position 531 (e.g., C531R, or 9 base pair duplication)
Amino acid position 532 (e.g., duplication)
Amino acid position 533 (e.g., G533C, G533S)
Amino acid position 550 (e.g., G550E)
Amino acid position 591 (e.g., V591I)
Amino acid position 593 (e.g., G593E)
Amino acid position 595 (e.g., E595D and E595A)
Amino acid position 600 (e.g., R600Q)
Amino acid position 602 (e.g., I602V)
Amino acid position 603 (e.g., K603Q, K603E)
Amino acid position 606 (e.g., Y606C)
Amino acid position 609 (e.g., C609Y, C609S, C609G, C609R, C609F, C609W)
Amino acid position 611 (e.g., C611R, C611S, C611G, C611Y, C611F, C611W)
Amino acid position 616 (e.g., E616Q)
Amino acid position 618 (e.g., C618S, C618Y, C618R, C618G, C618F, C618W)
Amino acid position 620 (e.g., C620S, C620W, C620R, C620G, C620L, C620Y, C620F)
Amino acid position 623 (e.g., E623K)
Amino acid position 624 (e.g., D624N)
Amino acid position 630 (e.g., C630A, C630R, C630S, C630Y, C630F, C630W)
Amino acid position 631 (e.g., D631N, D631Y, D631A, D631G, D631V, D631E,)
Amino acid position 632 (e.g., E632K, E632G)
Δ Amino acid residues 632-633 (6-Base Pair In-Frame Germline Deletion in Exon 11)
Amino acid position 633 (e.g., 9 base pair duplication)

Amino acid position 634 (e.g., C634W, C634Y, C634S, C634R, C634F, C634G, C634L, C634A, or C634T, or an insertion ELCR, or a 12 base pair duplication) (e.g., causing MTC)
Amino acid position 635 (e.g., R635G)
Amino acid position 636 (e.g., T636P, T636M)
Amino acid position 640 (e.g., A640G)
Amino acid position 641 (e.g., A641S, A641T)
Amino acid position 648 (e.g., V648I)
Amino acid position 649 (e.g., S649L)
Amino acid position 664 (e.g., A664D)
Amino acid position 665 (e.g., H665Q)
Amino acid position 666 (e.g., K666E, K666M, K666N, K666R)
Amino acid position 686 (e.g., S686N)
Amino acid position 689 (e.g., S689T)
Amino acid position 691 (e.g., G691S)
Amino acid position 694 (e.g., R694Q)
Amino acid position 700 (e.g., M700L)
Amino acid position 706 (e.g., V706M, V706A)
Amino acid position 713 splice variant (e.g., E713K)
Amino acid position 732 (e.g., E732K)
Amino acid position 736 (e.g., G736R)
Amino acid position 748 (e.g., G748C)
Amino acid position 750 (e.g., A750P)
Amino acid position 765 (e.g., S765P)
Amino acid position 766 (e.g., P766S, P766M)
Amino acid position 768 (e.g., E768Q, E768D)
Amino acid position 769 (e.g., L769L)
Amino acid position 770 (e.g., R770Q)
Amino acid position 771 (e.g., D771N)
Amino acid position 777 (e.g., N777S)
Amino acid position 778 (e.g., V778I)
Amino acid position 781 (e.g., Q781R)
Amino acid position 790 (e.g., L790F)
Amino acid position 791 (e.g., Y791F, Y791N)
Amino acid position 802
Amino acid position 804 (e.g., V804L, V804M, V804E) (e.g., causing MTC)
Amino acid position 805 (e.g., E805K)
Amino acid position 804/805 (e.g., V804M/E805K)
Amino acid position 806 (e.g., Y806F, Y806S, Y806G, Y806C, Y806E, Y806H, Y806N)
Amino acid position 810 (e.g., G810R, G810S, G810A, G810C, G810V, and G810D)

Amino acid position 818 (e.g., E818K)
Amino acid position 819 (e.g., S819I)
Amino acid position 823 (e.g., G823E)
Amino acid position 826 (e.g., Y826M, Y826S)
Amino acid position 833 (e.g., R833C)
Amino acid position 836 (e.g., S836S)
Amino acid position 841 (e.g., P841L, P841P)
Amino acid position 843 (e.g., E843D)
Amino acid position 844 (e.g., R844W, R844Q, R844L)
Amino acid position 848 (e.g., M848T)
Amino acid position 852 (e.g., I852M)
Amino acid position 865 (e.g., L865V)
Amino acid position 870 (e.g., L870F)
Amino acid position 873 (e.g., R873W)
Amino acid position 876 (e.g., A876V)
Amino acid position 881 (e.g., L881V)
Amino acid position 882
Amino acid position 883 (e.g., A883F, A883S, A883T)
Amino acid position 884 (e.g., E884K)
Amino acid position 886 (e.g., R886W)
Amino acid position 891 (e.g., S891A)
Amino acid position 897 (e.g., R897Q)
Amino acid position 898 (e.g., D898V)
Amino acid position 900 (e.g., Y900F)
Amino acid position 901 (e.g., E901K)
Amino acid position 904 (e.g., S904F, S904S, S904C)
Amino acid position 907 (e.g., K907E, K907M)
Amino acid position 908 (e.g., R908K)
Amino acid position 911 (e.g., G911D)
Amino acid position 912 (e.g., R912P, R912Q)
Amino acid position 918 (e.g., M918T, M918V, M918L) (e.g., causing MTC)
Amino acid position 919 (e.g., A919V)
Amino acid position 921 (e.g., E921K)
Amino acid position 922 (e.g., S922P, S922Y)
Amino acid position 930 (e.g., T930M)
Amino acid position 961 (e.g., F961L)
Amino acid position 972 (e.g., R972G)
Amino acid position 982 (e.g., R982C)
Amino acid position 1009 (e.g., M1009V)
Amino acid position 1015 (e.g., Y1015F)
Amino acid position 1017 (e.g., D1017N)
Amino acid position 1041 (e.g., V1041G)
Amino acid position 1064 (e.g., M1064T)

Amino acid position 1096 (e.g., Y1096F)
RET+3
(In-Frame Deletion in Exons 6 and 11)
(3bp In-Frame Deletion in Exon 15)

^AThe RET kinase mutations shown above may be activating mutations and/or may confer increased resistance of the RET kinase to a RET inhibitor and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wildtype RET kinase.

[00297] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes a splice variation in a RET mRNA which results in an expressed protein that is an alternatively spliced variant of RET having at least one residue deleted (as compared to the wild-type RET kinase) resulting in a constitutive activity of a RET kinase domain.

[00298] A “RET kinase inhibitor” as defined herein includes any compound exhibiting RET inhibition activity. In some embodiments, a RET kinase inhibitor is selective for a RET kinase. Exemplary RET kinase inhibitors can exhibit inhibition activity (IC₅₀) against a RET kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a RET kinase inhibitor can exhibit inhibition activity (IC₅₀) against a RET kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

[00299] As used herein, a “first RET kinase inhibitor” or “first RET inhibitor” is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as defined herein. As used herein, a “second RET kinase inhibitor” or a “second RET inhibitor” is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as defined herein. When both a first and a second RET inhibitor are present in a method provided herein, the first and second RET kinase inhibitor are different.

[00300] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions or insertions or deletions in a RET gene that results in the production of a RET kinase that has one or more

amino acids inserted or removed, as compared to the wild-type RET kinase. In some cases, the resulting RET kinase is more resistant to inhibition of its phosphotransferase activity by one or more first RET kinase inhibitor(s), as compared to a wildtype RET kinase or a RET kinase not including the same mutation. Such mutations, optionally, do not decrease the sensitivity of the cancer cell or tumor having the RET kinase to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof (e.g., as compared to a cancer cell or a tumor that does not include the particular RET inhibitor resistance mutation). In such embodiments, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased $V_{\max}$, a decreased K_m for ATP, and an increased K_D for a first RET kinase inhibitor, when in the presence of a first RET kinase inhibitor, as compared to a wildtype RET kinase or a RET kinase not having the same mutation in the presence of the same first RET kinase inhibitor.

[00301] In other embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions as compared to the wild-type RET kinase, and which has increased resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as compared to a wildtype RET kinase or a RET kinase not including the same mutation. In such embodiments, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased $V_{\max}$, a decreased K_m , and a decreased K_D in the presence of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as compared to a wildtype RET kinase or a RET kinase not having the same mutation in the presence of the same compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00302] Examples of RET inhibitor resistance mutations can, e.g., include point mutations, insertions, or deletions in and near the ATP binding site in the tertiary structure of RET kinase (e.g., amino acid positions 730-733, 738, 756, 758, 804, 805, 807, 810, 811, 881, and 892 of a wildtype RET kinase, e.g., the exemplary wildtype RET kinase described herein), including but not limited to a gatekeeper residue (e.g., amino acid position 804 in a wildtype RET kinase), P-loop residues (e.g., amino acid positions 730-737 in a wildtype RET kinase), residues in or near the DFG motif (e.g., amino acid positions 888-898 in a wildtype RET kinase), and ATP cleft

solvent front amino acid residues (e.g., amino acid positions 758, 811, and 892 of a wildtype RET kinase). Additional examples of these types of mutations include changes in residues that may affect enzyme activity and/or drug binding including but are not limited to residues in the activation loop (e.g., amino acid positions 891-916 of a wildtype RET kinase), residues near or interacting with the activation loop, residues contributing to active or inactive enzyme conformations, changes including mutations, deletions, and insertions in the loop proceeding the C-helix and in the C-helix (e.g., amino acid positions 768-788 in a wildtype RET protein). In some embodiments, the wildtype RET protein is the exemplary wildtype RET kinase described herein. Specific residues or residue regions that may be changed (and are RET inhibitor resistance mutations) include but are not limited to those listed in Table 3, with numbering based on the human wildtype RET protein sequence (e.g., SEQ ID NO: 1). As can be appreciated by those skilled in the art, an amino acid position in a reference protein sequence that corresponds to a specific amino acid position in SEQ ID NO: 1 can be determined by aligning the reference protein sequence with SEQ ID NO: 1 (e.g., using a software program, such as ClustalW2). Additional examples of RET inhibitor resistance mutation positions are shown in Table 4. Changes to these residues may include single or multiple amino acid changes, insertions within or flanking the sequences, and deletions within or flanking the sequences. See also J. Kooistra, G. K. Kanev, O. P. J. Van Linden, R. Leurs, I. J. P. De Esch, and C. De Graaf, “KLIFS: A structural kinase-ligand interaction database,” *Nucleic Acids Res.*, vol. 44, no. D1, pp. D365–D371, 2016.

[00303] Exemplary Sequence of Mature Human RET Protein (SEQ ID NO: 1)

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MAKATSGAAG LRLLLLLLLP LLGKVALGLY FSRDAYWEKL YVDQAAGTPL LYVHALRDAF EEVPSFRLGQ
HLYGTYRTRL HENNWICIQE DTGLLYLNRS LDHSSWEKLS VRNRGFPLLT VYLKVFLSPT SLREGECQWP
GCARVYFSFF NTSFPACSSL KPRELCFPET RPSFRIRENR PPGTFHQFRL LPVQFLCPNI SVAYRLLEGE
GLPFRCAPDS LEVSTRWALD REQREKYELV AVCTVHAGAR EEVVMVPFPV TVYDEDDSDAP TFPAGVDTAS
AVVEFKRKED TVVATLRVFD ADVVPASGEL VRRYTSTLLP GDTWAQQTFR VEHWPNETSV QANGSFVRAT
VHDYRLVLNR NLSISENRTM QLAVLVNDSF FQGPAGVLL LHFNVSVLPV SLHLPSTYSL SVSRRARREFA
QIGKVCVENC QAFSGINVQY KLHSSGANCS TLGVVTS AED TSGILFVNDT KALRRPKCAE LHYMVVATDQ
QTSRQAQAQL LVTVEGSYVA EEAGCPLSCA VSKRRLECEE CGGLGSPTGR CEWRQGDGKG ITRNFSTCSP
STKTCPDGHC DVVETQDINI CPQDCLRGSI VGGHEPGEP R GIKAGYGTCN CFPEEEKCFC EPEDIQDPLC
DELCRTVIAA AVLFSFIVSV LLSAFCIH CY HKFAHKPPIS SAEMTFRRPA QAFPVSYS S GARRPSLDSM
ENQVSVD A FK ILEDPKWEFP RKNLVLGKTL GEGEFGKVVK ATAFHLKGRA GYTTVAVKML KENASPSEL R
DLLSEFNV LK QVNHPHVIKL YGACSQDGPL LLIVEYAKYG SLRGFLRESR KVGPGYLGSG GSRNSSSLDH
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PDERALTMGD LISFAWQISQ GMQYLAEMKL VHRDLAARNI LVAEGRKMKI SDFGLSRDVY EEDSYVKRSQ
 GRIPVKWMAI ESLFDHIYTT QSDVWSFGVL LWEIVTLGGN PYPGIPPERL FNLLKTGHRM ERPDNCSEEM
 YRLMLQCWKQ EPDKRPVFAD ISKDLEKMMV KRRDYLDLAA STPSDSLIIYD DGLSEEETPL VDCNNAPLPR
 ALPSTWIENK LYGMSPDNWP GESPVPLTRA DGTNTGFPRY PNDSVYANWM LSPSAAKLMD TFDS

[00304] In some embodiments, a RET inhibitor resistance mutation can include a dysregulation of a MET gene, a MET kinase, or the expression or activity or level of any of the same.

[00305] The phrase "dysregulation of a MET gene, a MET kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., a MET gene translocation that results in the expression of a fusion protein, a deletion in a MET gene that results in the expression of a RET protein that includes a deletion of at least one amino acid as compared to the wild-type RET protein, or a mutation in a MET gene that results in the expression of a RET protein with one or more point mutations, or an alternative spliced version of a MET mRNA that results in a MET protein that results in the deletion of at least one amino acid in the MET protein as compared to the wild-type MET protein), or a MET gene amplification that results in overexpression of a MET protein or an autocrine activity resulting from the overexpression of a MET gene a cell, that results in a pathogenic increase in the activity of a kinase domain of a MET protein (e.g., a constitutively active kinase domain of a MET protein) in a cell. As another example, a dysregulation of a MET gene, a MET protein, or expression or activity, or level of any of the same, can be a mutation in a MET gene that encodes a MET protein that is constitutively active or has increased activity as compared to a protein encoded by a MET gene that does not include the mutation. For example, a dysregulation of a MET gene, a MET protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of MET that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not MET). In some examples, dysregulation of a MET gene, a MET protein, or expression or activity, can be a result of a gene translocation of one MET gene with another non-MET gene.

[00306] The term "wildtype MET" or "wild-type MET" describes a nucleic acid (e.g., a MET gene or a MET mRNA) or protein (e.g., a MET protein) that is found in a subject that does not have a MET-associated cancer (and optionally also does not have an increased risk of developing a MET-associated cancer and/or is not suspected of having a MET-associated cancer), or is found in a cell or tissue from a subject that does not have a MET-associated cancer (and optionally also does not have an increased risk of developing a MET-associated cancer and/or is not suspected of

having a MET-associated cancer). The term "MET-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a MET gene, a MET kinase, or expression or activity, or level of any of the same.

[00307] In some embodiments, compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof are useful in treating patients that develop cancers with RET inhibitor resistance mutations (e.g., that result in an increased resistance to a first RET inhibitor, e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D, and/or one or more RET inhibitor resistance mutations listed in Tables 3 and 4) by either dosing in combination or as a subsequent or additional (e.g., follow-up) therapy to existing drug treatments (e.g., other RET kinase inhibitors; e.g., first and/or second RET kinase inhibitors). Exemplary first and second RET kinase inhibitors are described herein. In some embodiments, a first or second RET kinase inhibitor can be selected from the group consisting of cabozantinib, vandetanib, alectinib, apatinib, sitravatinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864.

[00308] In some embodiments, compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof are useful for treating a cancer that has been identified as having one or more RET inhibitor resistance mutations (that result in an increased resistance to a first or second RET inhibitor, e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or e.g., a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D). In some embodiments, the one or more RET inhibitor resistance mutations occur in a nucleic acid sequence encoding a RET fusion protein (e.g. any of the RET gene fusion proteins described in Table 1) resulting in a RET fusion protein that exhibits RET kinase inhibitor resistance. In some embodiments, the one or more RET inhibitor resistance mutations occurs in a nucleic acid sequence encoding a mutant RET protein (e.g. a mutant RET protein having any of the mutations described in Table 2) resulting in a mutant RET protein that exhibits RET kinase resistance. Non-limiting examples of RET inhibitor resistance mutations are listed in Tables 3 and 4.

Table 3. RET Inhibitor Resistance Mutations

Exemplary RET Resistance Mutations
Amino acid position 634 (e.g., C634W) ¹⁰
Amino acid position 732 (e.g., E732K) ⁷
Amino acid position 788 (e.g., I788N) ⁸
Amino acid position 790 (e.g., L790F) ⁹
Amino acid position 804 (e.g., V804M ^{1,2} , V804L ^{1,2} , V804E ⁶)
Amino acid position 778/804 ¹³
Amino acid position 804/805 (e.g., V804M/E805K) ³
Amino acid position 806 (e.g., Y806C ^{4,6} , Y806E ⁴ , Y806S ⁶ , Y806H ⁶ , Y806N ⁶)
Amino acid position 804/806 (e.g., V804M/Y806C) ¹¹
Amino acid position 810 (e.g., G810A ⁵ , G810R ⁶ , G810S ⁶ , G810C, G810V, and G810D)
Amino acid position 865 (e.g., L865V ⁶)
Amino acid position 870 (e.g., L870F ⁶)
Amino acid position 891 (e.g., S891A) ¹⁰
Amino acid position 904 (e.g., S904F) ¹²
Amino acid position 804/904 (e.g., V804M/S904C) ¹¹
Amino acid position 918 (e.g., M918T) ¹⁰

¹ Yoon et al., *J. Med. Chem.* 59(1):358-73, 2016.

² U.S. Patent No. 8,629,135.

³ Cranston, et al., *Cancer Res.* 66(20):10179-87, 2006.

⁴ Carlomagno, et al., *Endocr. Rel. Cancer* 16(1):233-41, 2009.

⁵ Huang et al., *Mol. Cancer Ther.*, 2016 Aug 5. pii: molcanther.0258.2016. [Epub ahead of print].

⁶ PCT Patent Application Publication No. WO 2016/127074.

⁷ Mamedova et al., Summer Undergraduate Research Programs (SURP) Student Abstracts, University of Oklahoma Health Sciences Center, 2016.

⁸ Plenker et al., *Sci. Transl. Med.*, 9(394), doi: 10.1126/scitranslmed.aah6144, 2017.

⁹ Kraft et al., *Cancer Research*, 2017, Vol. 77, No. 13, Supp. Supplement 1. Abstract Number: 4882; American Association for Cancer Research Annual Meeting 2017. Washington, DC, United States. 01 Apr 2017-05 Apr 2017.

¹⁰ U.S. Patent Application Publication No. 2018/0022732.

¹¹ Roskoski and Sadeghi-Nejad, *Pharmacol. Res.*, 128, 1-17. doi: 10.1016/j.phrs.2017.12.021, 2018.

¹² Nakaoku, et al. *Nat Commun*, 9(1), 625. doi: 10.1038/s41467-018-02994-7, 2018.

¹³ Roy et al. *Oncologist*, 18(10): 1093-1100. doi: 10.1634/theoncologist.2013-0053, 2013.

Table 4. Additional Exemplary Amino Acid Positions of RET Inhibitor Resistance Mutations

RET Amino Acid and Position	Exemplary Mutation	Mechanistic Resistance Rationale
L730	P	Steric hindrance and/or active conformational effect
G731	V	Steric hindrance and/or active conformational effect
E732	K	Steric hindrance and/or active conformational effect
G733	V	Steric hindrance and/or active conformational effect
E734	K	Steric hindrance and/or active conformational effect
L760	M	Active conformational effect
K761	E	Active conformational effect
E762	K	Active conformational effect
N763	D	Active conformational effect
A764	V	Active conformational effect
S765	N	Active conformational effect
P766	A	Active conformational effect
S767	C	Active conformational effect
E768	K	Active conformational effect
L779	M	Steric hindrance and/or active conformational effect
I788	M	Steric hindrance and/or active conformational effect
M868	R	Steric hindrance and/or active conformational effect
K869	E	Steric hindrance and/or active conformational effect
L870	Q	Steric hindrance and/or active conformational effect
V871	M	Steric hindrance and/or active conformational effect
H872	R	Steric hindrance and/or active conformational effect
R873	P	Steric hindrance and/or active conformational effect
D874	Y	Steric hindrance and/or active conformational effect
L881	R	Steric hindrance and/or active conformational effect
L895	M	Active conformational effect

S896	N	Active conformational effect
R897	C	Active conformational effect
D898	Y	Active conformational effect
V899	G	Active conformational effect
Y900	D	Active conformational effect
E901	K	Active conformational effect
E902	K	Active conformational effect
D903	Y	Active conformational effect
S904	C	Active conformational effect
Y905	D	Active conformational effect
V906	M	Active conformational effect
K907	E	Active conformational effect
R908	P	Active conformational effect
S909	C	Active conformational effect
Q910	R	Active conformational effect
G911	C	Active conformational effect
R912	P	Active conformational effect

[00309] The oncogenic role of RET was first described in papillary thyroid carcinoma (PTC) (Grieco et al., *Cell*, 1990, 60, 557-63), which arises from follicular thyroid cells and is the most common thyroid malignancy. Approximately 20-30% of PTC harbor somatic chromosomal rearrangements (translocations or inversions) linking the promoter and the 5' portions of constitutively expressed, unrelated genes to the RET tyrosine kinase domain (Greco et al., *Q. J. Nucl. Med. Mol. Imaging*, 2009, 53, 440-54), therefore driving its ectopic expression in thyroid cells. Fusion proteins generated by such rearrangements are termed “RET/PTC” proteins. For example, RET/PTC 1 is a fusion between CCDD6 and RET that is commonly found in papillary thyroid carcinomas. Similarly, both RET/PTC3 and RET/PTC4 are fusions of ELE1 and RET that are commonly found in papillary thyroid carcinomas, although the fusion events resulting RET/PTC3 and RET/PTC4 lead to different proteins with different molecular weights (see e.g., Fugazzola et al., *Oncogene*, 13(5):1093-7, 1996). Some RET fusions associated with PTC are not referred to as “RET/PTC”, but instead are referred to as the the fusion protein itself. For example,

fusion between RET and both ELKS and PCM1 are found in PTCs, but the fusion proteins are referred to as ELKS-RET and PCM1-RET (see e.g., Romei and Elisei, *Front. Endocrinol. (Lausanne)*, 3:54, doi: 10.3389/fendo.2012.00054, 2012). The role of RET-PTC rearrangements in the pathogenesis of PTC has been confirmed in transgenic mice (Santoro et al., *Oncogene*, 1996, 12, 1821-6). To date, a variety of fusion partners have been identified, from PTC and other cancer types, all providing a protein/protein interaction domain that induces ligand-independent RET dimerization and constitutive kinase activity (see, e.g., Table 1). Recently, a 10.6 Mb pericentric inversion in chromosome 10, where RET gene maps, has been identified in about 2% of lung adenocarcinoma patients, generating different variants of the chimeric gene KIF5B-RET (Ju et al., *Genome Res.*, 2012, 22, 436-45; Kohno et al., 2012, *Nature Med.*, 18, 375-7; Takeuchi et al., *Nature Med.*, 2012, 18, 378-81; Lipson et al., 2012, *Nature Med.*, 18, 382-4). The fusion transcripts are highly expressed and all the resulting chimeric proteins contain the N-terminal portion of the coiled-coil region of KIF5B, which mediates homodimerization, and the entire RET kinase domain. None of RET positive patients harbor other known oncogenic alterations (such as EGFR or K-Ras mutation, ALK translocation), supporting the possibility that KIF5B-RET fusion could be a driver mutation of lung adenocarcinoma. The oncogenic potential of KIF5B-RET has been confirmed by transfecting the fusion gene into cultured cell lines: similarly to what has been observed with RET-PTC fusion proteins, KIF5B-RET is constitutively phosphorylated and induces NIH-3T3 transformation and IL-3 independent growth of BA-F3 cells. However, other RET fusion proteins have been identified in lung adenocarcinoma patients, such as the CCDC6-RET fusion protein, which has been found to play a key role in the proliferation of the human lung adenocarcinoma cell line LC-2/ad (*Journal of Thoracic Oncology*, 2012, 7(12):1872-1876). RET inhibitors have been shown to be useful in treating lung cancers involving RET rearrangements (Drilon, A.E. et al. *J Clin Oncol* 33, 2015 (suppl; abstr 8007)). RET fusion proteins have also been identified in patients having colorectal cancer (Song Eun-Kee, et al. *International Journal of Cancer*, 2015, 136: 1967-1975).

[00310] Besides rearrangements of the RET sequence, gain of function point mutations of RET proto-oncogene are also driving oncogenic events, as shown in medullary thyroid carcinoma (MTC), which arises from parafollicular calcitonin-producing cells (de Groot, et al., *Endocrine Rev.*, 2006, 27, 535-60; Wells and Santoro, *Clin. Cancer Res.*, 2009, 15, 7119-7122). Around 25% of MTC are associated with multiple endocrine neoplasia type 2 (MEN2), a group of inherited

cancer syndromes affecting neuroendocrine organs caused by germline activating point mutations of RET. In MEN2 subtypes (MEN2A, MEN2B and Familial MTC/FMTC) RET gene mutations have a strong phenotype-genotype correlation defining different MTC aggressiveness and clinical manifestations of the disease. In MEN2A syndrome mutations involve one of the six cysteine residues (mainly C634) located in the cysteine-rich extracellular region, leading to ligand-independent homodimerization and constitutive RET activation. Patients develop MTC at a young age (onset at 5-25 years) and may also develop pheochromocytoma (50%) and hyperparathyroidism. MEN2B is mainly caused by M918T mutation, which is located in the kinase domain. This mutation constitutively activates RET in its monomeric state and alters substrate recognition by the kinase. MEN2B syndrome is characterized by an early onset (< 1 year) and very aggressive form of MTC, pheochromocytoma (50% of patients) and ganglioneuromas. In FMTC the only disease manifestation is MTC, usually occurring at an adult age. Many different mutations have been detected, spanning the entire RET gene. The remaining 75% of MTC cases are sporadic and about 50% of them harbor RET somatic mutations: the most frequent mutation is M918T that, as in MEN2B, is associated with the most aggressive phenotype. Somatic point mutations of RET have also been described in other tumors such as colorectal cancer (Wood et al., *Science*, 2007, 318, 1108-13) and small cell lung carcinoma (*Jpn. J. Cancer Res.*, 1995, 86, 1127-30). In some embodiments, the MTC is RET-fusion positive MTC.

[00311] RET signaling components have been found to be expressed in primary breast tumors and to functionally interact with estrogen receptor-cc pathway in breast tumor cell lines (Boulay et al., *Cancer Res.* 2008, 68, 3743-51; Plaza-Menacho et al., *Oncogene*, 2010, 29, 4648-57), while RET expression and activation by GDNF family ligands could play an important role in perineural invasion by different types of cancer cells (Ito et al., *Surgery*, 2005, 138, 788-94; Gil et al., *J. Natl. Cancer Inst.*, 2010, 102, 107-18; Iwahashi et al., *Cancer*, 2002, 94, 167-74).

[00312] RET is also expressed in 30-70% of invasive breast cancers, with expression being relatively more frequent in estrogen receptor-positive tumors (Plaza-Menacho, I., et al., *Oncogene*, 2010, 29, 4648-4657; Esseghir, S., et al., *Cancer Res.*, 2007, 67, 11732-11741; Morandi, A., et al., *Cancer Res.*, 2013, 73, 3783-3795; Gattelli, A., *EMBO Mol. Med.*, 2013, 5, 1335-1350).

[00313] The identification of RET rearrangements has been reported in a subset of (patient-derived xenograft) PDX established from colorectal cancer. Although the frequency of such events in colorectal cancer patients remains to be defined, these data suggest a role of RET as a target in

this indication (Gozgit et al., AACR Annual Meeting 2014). Studies have shown that the RET promoter is frequently methylated in colorectal cancers, and heterozygous missense mutations, which are predicted to reduce RET expression, are identified in 5-10% of cases, which suggests that RET might have some features of a tumor suppressor in sporadic colon cancers (Luo, Y., et al., *Oncogene*, 2013, 32, 2037-2047; Sjoblom, T., et al., *Science*, 2006, 268-274; Cancer Genome Atlas Network, *Nature*, 2012, 487, 330-337).

[00314] An increasing number of tumor types are now being shown to express substantial levels of wild-type RET kinase that could have implications for tumor progression and spread. RET is expressed in 50-65% of pancreatic ductal carcinomas, and expression is more frequent in metastatic and higher grade tumors (Ito, Y., et al., *Surgery*, 2005, 138, 788-794; Zeng, Q., et al., *J. Int. Med. Res.* 2008, 36, 656-664).

[00315] In neoplasms of hematopoietic lineages, RET is expressed in acute myeloid leukemia (AML) with monocytic differentiation, as well as in CMML (Gattei, V. et al., *Blood*, 1997, 89, 2925-2937; Gattei, V., et al., *Ann. Hematol*, 1998, 77, 207-210; Camos, M., *Cancer Res.* 2006, 66, 6947-6954). Recent studies have identified rare chromosomal rearrangements that involve RET in patients with chronic myelomonocytic leukemia (CMML). CMML is frequently associated with rearrangements of several tyrosine kinases, which result in the expression of chimeric cytosolic oncoproteins that lead to activation of RAS pathways (Kohlmann, A., et al., *J. Clin. Oncol.* 2010, 28, 2858-2865). In the case of RET, gene fusions that link RET with BCR (BCR-RET) or with fibroblast growth factor receptor 1 oncogene partner (FGFR1OP-RET) were transforming in early hematopoietic progenitor cells and could shift maturation of these cells towards monocytic paths, probably through the initiation of RET-mediated RAS signaling (Ballerini, P., et al., *Leukemia*, 2012, 26, 2384-2389).

[00316] RET expression has also been shown to occur in several other tumor types, including prostate cancer, small-cell lung carcinoma, melanoma, renal cell carcinoma, and head and neck tumors (Narita, N., et al., *Oncogene*, 2009, 28, 3058-3068; Mulligan, L. M., et al., *Genes Chromosomes Cancer*, 1998, 21, 326-332; Flavin, R., et al., *Urol. Oncol.*, 2012, 30, 900-905; Dawson, D. M., *J Natl Cancer Inst*, 1998, 90, 519-523).

[00317] In neuroblastoma, RET expression and activation by GFLs has roles in tumor cell differentiation, potentially collaborating with other neurotrophic factor receptors to down regulate N-Myc, the expression of which is a marker of poor prognosis (Hofstra, R. M., W., et al., *Hum.*

Genet. 1996, 97, 362-364; Petersen, S. and Bogenmann, E., *Oncogene*, 2004, 23, 213-225; Brodeur, G. M., *Nature Ref. Cancer*, 2003, 3, 203-216).

[00318] Multitargeted inhibitors which cross react with RET are known (Borrello, M.G., et al., *Expert Opin. Ther. Targets*, 2013, 17(4), 403-419; International Patent Application Nos. WO 2014/141187, WO 2014/184069, and WO 2015/079251). Such multitargeted inhibitors (or multikinase inhibitors or MKIs) can also be associated with development of RET inhibitor resistance mutations. See, for example, Q. Huang et al., "Preclinical Modeling of KIF5B-RET Fusion Lung Adenocarcinoma,," *Mol. Cancer Ther.*, no. 18, pp. 2521-2529, 2016; Yasuyuki Kaneta et al., Abstract B173: Preclinical characterization and antitumor efficacy of DS-5010, a highly potent and selective RET inhibitor, *Mol Cancer Ther* January 1 2018 (17) (1 Supplement) B173; DOI:10.1158/1535-7163.TARG-17-B173.

[00319] Accordingly, provided herein are methods for treating a patient diagnosed with (or identified as having) a cancer that include administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. Also provided herein are methods for treating a patient identified or diagnosed as having a RET-associated cancer that include administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof. In some embodiments, the patient that has been identified or diagnosed as having a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is a RET-associated cancer. For example, the RET-associated cancer can be a cancer that includes one or more RET inhibitor resistance mutations.

[00320] Also provided are methods for treating cancer in a patient in need thereof, the method comprising: (a) detecting a RET-associated cancer in the patient; and (b) administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof. Some embodiments of these methods further include administering to the subject another

anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or an immunotherapy). In some embodiments, the subject was previously treated with a first RET inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of the tumor or radiation therapy. In some embodiments, the patient is determined to have a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is a RET-associated cancer. For example, the RET-associated cancer can be a cancer that includes one or more RET inhibitor resistance mutations.

[00321] Also provided are methods of treating a patient that include performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and administering (e.g., specifically or selectively administering) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof to the patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy). In some embodiments of these methods, the subject was previously treated with a first RET inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of a tumor or radiation therapy. In some embodiments, the patient is a patient suspected of having a RET-associated cancer, a patient presenting with one or more symptoms of a RET-associated cancer, or a patient having an elevated risk of developing a RET-associated cancer. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. Additional, non-limiting assays that may be used in these methods are described herein. Additional assays are also known in the art. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of

any of the same includes one or more RET inhibitor resistance mutations.

[00322] Also provided is a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof for use in treating a RET-associated cancer in a patient identified or diagnosed as having a RET-associated cancer through a step of performing an assay (e.g., an in vitro assay) on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, where the presence of a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, identifies that the patient has a RET-associated cancer. Also provided is the use of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for the manufacture of a medicament for treating a RET-associated cancer in a patient identified or diagnosed as having a RET-associated cancer through a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same where the presence of dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, identifies that the patient has a RET-associated cancer. Some embodiments of any of the methods or uses described herein further include recording in the patient's clinical record (e.g., a computer readable medium) that the patient is determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, through the performance of the assay, should be administered a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[00323] Also provided is a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, for use in the treatment of a cancer in a patient in need thereof or a patient identified or diagnosed as having a RET-associated cancer. Also provided is the use of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for the manufacture of a medicament for treating a cancer in a patient

identified or diagnosed as having a RET-associated cancer. In some embodiments, the cancer is a RET-associated cancer, for example, a RET-associated cancer having one or more RET inhibitor resistance mutations. In some embodiments, a patient is identified or diagnosed as having a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the sample. As provided herein, a RET-associated cancer includes those described herein and known in the art.

[00324] In some embodiments of any of the methods or uses described herein, the patient has been identified or diagnosed as having a cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient has a tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient can be a patient with a tumor(s) that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient can be a patient whose tumors have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient is suspected of having a RET-associated cancer (e.g., a cancer having one or more RET inhibitor resistance mutations). In some embodiments, provided herein are methods for treating a RET-associated cancer in a patient in need of such treatment, the method comprising a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more fusion proteins. Non-limiting examples of RET gene fusion proteins are described in Table 1. In some embodiments, the fusion protein is KIF5B-RET. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET kinase protein point mutations/insertions/deletions. Non-limiting examples of RET kinase protein point mutations/insertions/deletions are described in Tables 2 and 2a. In some embodiments, the RET kinase protein point mutations/insertions/deletions are selected from the group consisting of

M918T, M918V, C634W, V804L, V804M, G810S, and G810R. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. Non-limiting examples of RET inhibitor resistance mutations are described in Tables 3 and 4. In some embodiments, the RET inhibitor resistance mutation is V804M. In some embodiments, the RET inhibitor resistance mutation is G810S. In some embodiments, the RET inhibitor resistance mutation is G810R. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a tumor positive for one or more RET inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

[00325] In some embodiments of any of the methods or uses described herein, the patient has a clinical record indicating that the patient has a tumor that has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same (e.g., a tumor having one or more RET inhibitor resistance mutations). In some embodiments, the clinical record indicates that the patient should be treated with one or more of the compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or compositions provided herein. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a cancer having one or more RET inhibitor resistance mutations. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a tumor positive for one or more RET inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

[00326] Also provided are methods of treating a patient that include administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable

salt, amorphous, or polymorph form thereof to a patient having a clinical record that indicates that the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Also provided is the use of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for the manufacture of a medicament for treating a RET-associated cancer in a patient having a clinical record that indicates that the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Some embodiments of these methods and uses can further include: a step of performing an assay (e.g., an in vitro assay) on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and recording the information in a patient's clinical file (e.g., a computer readable medium) that the patient has been identified to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the dysregulation of a RET gene, RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[00327] Also provided herein is a method of treating a subject. In some embodiments, the method includes performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a RET gene, a RET protein, or expression or level of any of the same. In some such embodiments, the method also includes administering to a subject determined to have a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the method includes determining that a subject has a dysregulation of a RET gene, a RET protein, or expression or level of any of the same via an assay performed on a sample obtained from the subject. In such embodiments, the method also includes administering to a subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the dysregulation in a RET gene, a RET kinase protein, or expression or activity of the same is a gene or chromosome translocation that results in the expression of a RET fusion protein (e.g., any of the RET fusion proteins described herein). In

some embodiments, the RET fusion can be selected from a KIF5B-RET fusion and a CCDC6-RET fusion. In some embodiments, the dysregulation in a RET gene, a RET kinase protein, or expression or activity or level of any of the same is one or more point mutation in the RET gene (e.g., any of the one or more of the RET point mutations described herein). The one or more point mutations in a RET gene can result, e.g., in the translation of a RET protein having one or more of the following amino acid substitutions: M918T, M918V, C634W, V804L, V804M, G810S, and G810R. In some embodiments, the dysregulation in a RET gene, a RET kinase protein, or expression or activity or level of any of the same is one or more RET inhibitor resistance mutations (e.g., any combination of the one or more RET inhibitor resistance mutations described herein). Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second RET inhibitor a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy).

[00328] In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier and inhibiting a RET kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a patient with cancer (e.g., a RET-associated cancer such as a RET-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the patient. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, the compounds can be used in the treatment of one or more of gliomas such as glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas, meningiomas, medulloblastomas, gangliogliomas, schwannomas (neurilemmomas), and craniopharyngiomas (see, for example, the tumors listed in Louis, D.N. et al. *Acta Neuropathol* 131(6), 803-820 (June 2016)). In some embodiments, the brain tumor is a primary brain tumor. In some embodiments, the patient has previously been treated with another anticancer agent, e.g., another RET inhibitor (e.g., a compound that is not a compound of General Formula I) or a multi-kinase inhibitor. In some embodiments, the brain tumor is a metastatic brain tumor. In some embodiments, the patient has previously been treated with another anticancer agent, e.g., another RET inhibitor (e.g., a compound that is not a compound of General Formula I) or a multi-kinase inhibitor.

[00329] Also provided are methods (e.g., in vitro methods) of selecting a treatment for a patient identified or diagnosed as having a RET-associated cancer. Some embodiments can further include administering the selected treatment to the patient identified or diagnosed as having a RET-associated cancer. For example, the selected treatment can include administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. Some embodiments can further include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and identifying and diagnosing a patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, as having a RET-associated cancer. In some embodiments, the cancer is a RET-associated cancer having one or more RET inhibitor resistance mutations. In some embodiments, the patient has been identified or diagnosed as having a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient. In some embodiments, the RET-associated cancers is a cancer described herein or known in the art. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes the next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy.

[00330] Also provided herein are methods of selecting a treatment for a patient, wherein the methods include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same (e.g., one or more RET inhibitor resistance mutations), and identifying or diagnosing a patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, as having a RET-associated cancer. Some embodiments further include administering the selected treatment to the patient identified or diagnosed as having a RET-associated cancer. For example, the selected treatment can include administration of a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the patient identified or diagnosed as having a RET-associated cancer. In some embodiments, the assay is an in vitro

assay. For example, an assay that utilizes the next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy.

[00331] Also provided are methods of selecting a patient for treatment, wherein the methods include selecting, identifying, or diagnosing a patient having a RET-associated cancer, and selecting the patient for treatment including administration of a therapeutically-effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, identifying or diagnosing a patient as having a RET-associated cancer can include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and identifying or diagnosing a patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, as having a RET-associated cancer. In some embodiments, the method of selecting a patient for treatment can be used as a part of a clinical study that includes administration of various treatments of a RET-associated cancer. In some embodiments, a RET-associated cancer is a cancer having one or more RET inhibitor resistance mutations. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes the next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the dysregulation of the RET gene, the RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[00332] In some embodiments of any of the methods or uses described herein, an assay used to determine whether the patient has a dysregulation of a RET gene, or a RET kinase, or expression or activity or level of any of the same, using a sample from a patient can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting dysregulation of a RET gene, a RET kinase, or expression or activity or levels of any of the same (see, e.g., the references cited herein). In some embodiments, the

dysregulation of the RET gene, the RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the patient. In some embodiments, the patient is a patient suspected of having a RET-associated cancer, a patient having one or more symptoms of a RET-associated cancer, and/or a patient that has an increased risk of developing a RET-associated cancer).

[00333] In some embodiments, dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same can be identified using a liquid biopsy (variously referred to as a fluid biopsy or fluid phase biopsy). See, e.g., Karachialiou et al., “Real-time liquid biopsies become a reality in cancer treatment”, *Ann. Transl. Med.*, 3(3):36, 2016. Liquid biopsy methods can be used to detect total tumor burden and/or the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same. Liquid biopsies can be performed on biological samples obtained relatively easily from a subject (e.g., via a simple blood draw) and are generally less invasive than traditional methods used to detect tumor burden and/or dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same. In some embodiments, liquid biopsies can be used to detect the presence of dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same at an earlier stage than traditional methods. In some embodiments, the biological sample to be used in a liquid biopsy can include, blood, plasma, urine, cerebrospinal fluid, saliva, sputum, broncho-alveolar lavage, bile, lymphatic fluid, cyst fluid, stool, ascites, and combinations thereof. In some embodiments, a liquid biopsy can be used to detect circulating tumor cells (CTCs). In some embodiments, a liquid biopsy can be used to detect cell-free DNA. In some embodiments, cell-free DNA detected using a liquid biopsy is circulating tumor DNA (ctDNA) that is derived from tumor cells. Analysis of ctDNA (e.g., using sensitive detection techniques such as, without limitation, next-generation sequencing (NGS), traditional PCR, digital PCR, or microarray analysis) can be used to identify dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same.

[00334] In some embodiments, ctDNA derived from a single gene can be detected using a liquid biopsy. In some embodiments, ctDNA derived from a plurality of genes (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more, or any number of genes in between these numbers) can be detected using a liquid biopsy. In some embodiments, ctDNA derived from a plurality of genes can be detected using any of a variety of commercially-

available testing panels (e.g., commercially-available testing panels designed to detect dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same). Liquid biopsies can be used to detect dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same including, without limitation, point mutations or single nucleotide variants (SNVs), copy number variants (CNVs), genetic fusions (e.g., translocations or rearrangements), insertions, deletions, or any combination thereof. In some embodiments, a liquid biopsy can be used to detect a germline mutation. In some embodiments, a liquid biopsy can be used to detect a somatic mutation. In some embodiments, a liquid biopsy can be used to detect a primary genetic mutation (e.g., a primary mutation or a primary fusion that is associated with initial development of a disease, e.g., cancer). In some embodiments, a liquid biopsy can be used to detect a genetic mutation that develops after development of the primary genetic mutation (e.g., a resistance mutation that arises in response to a treatment administered to a subject). In some embodiments, a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same identified using a liquid biopsy is also present in a cancer cell that is present in the subject (e.g., in a tumor). In some embodiments, any of the types of dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same described herein can be detected using a liquid biopsy. In some embodiments, a genetic mutation identified via a liquid biopsy can be used to identify the subject as a candidate for a particular treatment. For example, detection of dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in the subject can indicate that the subject will be responsive to a treatment that includes administration of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00335] Liquid biopsies can be performed at multiple times during a course of diagnosis, a course of monitoring, and/or a course of treatment to determine one or more clinically relevant parameters including, without limitation, progression of the disease, efficacy of a treatment, or development of resistance mutations after administering a treatment to the subject. For example, a first liquid biopsy can be performed at a first time point and a second liquid biopsy can be performed at a second time point during a course of diagnosis, a course of monitoring, and/or a course of treatment. In some embodiments, the first time point can be a time point prior to diagnosing a subject with a disease (e.g., when the subject is healthy), and the second time point can be a time point after subject has developed the disease (e.g., the second time point can be used

to diagnose the subject with the disease). In some embodiments, the first time point can be a time point prior to diagnosing a subject with a disease (e.g., when the subject is healthy), after which the subject is monitored, and the second time point can be a time point after monitoring the subject. In some embodiments, the first time point can be a time point after diagnosing a subject with a disease, after which a treatment is administered to the subject, and the second time point can be a time point after the treatment is administered; in such cases, the second time point can be used to assess the efficacy of the treatment (e.g., if the genetic mutation(s) detected at the first time point are reduced in abundance or are undetectable) or to determine the presence of a resistance mutation that has arisen as a result of the treatment. In some embodiments, a treatment to be administered to a subject can include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00336] In some embodiments, the efficacy of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, can be determined by assessing the allele frequency of a dysregulation of a RET gene in cfDNA obtained from a patient at different time points, e.g., cfDNA obtained from the patient at a first time point and cfDNA obtained from the patient at a second time point, where at least one dose of a compound of Formula I-IV is administered to the patient between the first and second time points. Some embodiments of these methods can further include administering to the patient the at least one dose of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, between the first and second time points. For example, a reduction (e.g., a 1% to about a 99% reduction, a 1% to about a 95% reduction, a 1% to about a 90% reduction, a 1% to about a 85% reduction, a 1% to about a 80% reduction, a 1% to about a 75% reduction, a 1% reduction to about a 70% reduction, a 1% reduction to about a 65% reduction, a 1% reduction to about a 60% reduction, a 1% reduction to about a 55% reduction, a 1% reduction to about a 50% reduction, a 1% reduction to about a 45% reduction, a 1% reduction to about a 40% reduction, a 1% reduction to about a 35% reduction, a 1% reduction to about a 30% reduction, a 1% reduction to about a 25% reduction, a 1% reduction to about a 20% reduction, a 1% reduction to about a 15% reduction, a 1% reduction to about a 10% reduction, a 1% to about a 5% reduction, about a 5% to about a 99% reduction, about a 10% to about a 99% reduction, about a 15% to about a 99% reduction, about a 20% to about a 99% reduction, about a 25% to about a 99% reduction, about a 30% to about a 99% reduction, about a 35% to about a 99% reduction, about a 40% to about a 99%

reduction, about a 45% to about a 99% reduction, about a 50% to about a 99% reduction, about a 55% to about a 99% reduction, about a 60% to about a 99% reduction, about a 65% to about a 99% reduction, about a 70% to about a 99% reduction, about a 75% to about a 95% reduction, about a 80% to about a 99% reduction, about a 90% reduction to about a 99% reduction, about a 95% to about a 99% reduction, about a 5% to about a 10% reduction, about a 5% to about a 25% reduction, about a 10% to about a 30% reduction, about a 20% to about a 40% reduction, about a 25% to about a 50% reduction, about a 35% to about a 55% reduction, about a 40% to about a 60% reduction, about a 50% reduction to about a 75% reduction, about a 60% reduction to about 80% reduction, or about a 65% to about a 85% reduction) in the allele frequency (AF) of the dysregulation of a RET gene in the cfDNA obtained from the patient at the second time point as compared to the allele frequency (AF) of the dysregulation of a RET gene in the cfDNA obtained from the patient at the first time point indicates that the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, was effective in the subject. In some embodiments, the AF is reduced such that the level is below the detection limit of the instrument. Alternatively, an increase in the allele frequency (AF) of the dysregulation of a RET gene in the cfDNA obtained from the patient at the second time point as compared to the allele frequency (AF) of the dysregulation of a RET gene in the cfDNA obtained from the patient at the first time point indicates that the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, was not effective in the subject (e.g., the subject has developed a resistance mutation to the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof). Some embodiments of these methods can further include, administering additional doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, to a patient in which a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, was determined to be effective. Some embodiments of these methods can further include, administering a different treatment (e.g., a treatment that does not include the administration of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy) to a patient in which a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, was determined not to be effective.

[00337] In some examples of these methods, the time difference between the first and second

time points can be about 1 day to about 1 year, about 1 day to about 11 months, about 1 day to about 10 months, about 1 day to about 9 months, about 1 day to about 8 months, about 1 day to about 7 months, about 1 day to about 6 months, about 1 day to about 5 months, about 1 day to about 4 months, about 1 day to about 3 months, about 1 day to about 10 weeks, about 1 day to about 2 months, about 1 day to about 6 weeks, about 1 day to about 1 month, about 1 day to about 25 days, about 1 day to about 20 days, about 1 day to about 15 days, about 1 day to about 10 days, about 1 day to about 5 days, about 2 days to about 1 year, about 5 days to about 1 year, about 10 days to about 1 year, about 15 days to about 1 year, about 20 days to about 1 year, about 25 days to about 1 year, about 1 month to about 1 year, about 6 weeks to about 1 year, about 2 months to about 1 year, about 3 months to about 1 year, about 4 months to about 1 year, about 5 months to about 1 year, about 6 months to about 1 year, about 7 months to about 1 year, about 8 months to about 1 year, about 9 months to about 1 year, about 10 months to about 1 year, about 11 months to about 1 year, about 1 day to about 7 days, about 1 day to about 14 days, about 5 days to about 10 days, about 5 day to about 20 days, about 10 days to about 20 days, about 15 days to about 1 month, about 15 days to about 2 months, about 1 week to about 1 month, about 2 weeks to about 1 month, about 1 month to about 3 months, about 3 months to about 6 months, about 4 months to about 6 months, about 5 months to about 8 months, or about 7 months to about 9 months. In some embodiments of these methods, the patient can be previously identified as having a cancer having a dysregulated RET gene (e.g., any of the examples of a dysregulated RET gene described herein). In some embodiments of these methods, a patient can have been previously diagnosed as having any of the types of cancer described herein. In some embodiments of these methods, the patient can have one or more metastases (e.g., one or more brain metastases).

[00338] In some of the above embodiments, the cfDNA comprises ctDNA such as RET-associated ctDNA. For example, the cfDNA is ctDNA such as RET-associated ctDNA. In some embodiments, at least some portion of cfDNA is determined to be RET-associated ctDNA, for example, a sequenced and/or quantified amount of the total cfDNA is determined to have a RET fusion and/or a RET resistance mutation.

[00339] In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment or therapy in addition to compositions provided herein may be, for example, surgery, radiotherapy, and chemotherapeutic agents, such as other kinase inhibitors,

signal transduction inhibitors and/or monoclonal antibodies. For example, a surgery may be open surgery or minimally invasive surgery. Compounds of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof therefore may also be useful as adjuvants to cancer treatment, that is, they can be used in combination with one or more additional therapies or therapeutic agents, for example a chemotherapeutic agent that works by the same or by a different mechanism of action. In some embodiments, a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, can be used prior to administration of an additional therapeutic agent or additional therapy. For example, a patient in need thereof can be administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for a period of time and then under go at least partial resection of the tumor. In some embodiments, the treatment with one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof reduces the size of the tumor (e.g., the tumor burden) prior to the at least partial resection of the tumor. In some embodiments, a patient in need thereof can be administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for a period of time and under one or more rounds of radiation therapy. In some embodiments, the treatment with one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof reduces the size of the tumor (e.g., the tumor burden) prior to the one or more rounds of radiation therapy.

[00340] In some embodiments, a patient has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to standard therapy (e.g., administration of a chemotherapeutic agent, such as a first RET inhibitor or a multikinase inhibitor, immunotherapy, or radiation (e.g., radioactive iodine)). In some embodiments, a patient has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to prior therapy (e.g., administration of a chemotherapeutic agent, such as a first RET inhibitor or a multikinase inhibitor, immunotherapy, or radiation (e.g., radioactive iodine)). In some embodiments, a patient has a cancer (e.g., a locally advanced or metastatic tumor) that has no standard therapy. In some embodiments, a patient is RET-kinase inhibitor naïve. For example, the patient is naïve to treatment with a selective RET-kinase inhibitor. In some embodiments, a patient is not RET-kinase inhibitor naïve.

[00341] In some embodiments, a patient has undergone prior therapy. In some embodiments, a patient having NSCLC (e.g., a RET-fusion positive NSCLC) has received treatment with a platinum-based chemotherapy, PD-1/PDL1 immunotherapy, or both prior to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, a patient having a thyroid cancer (e.g., a RET-fusion positive thyroid cancer) has received treatment with one or more of sorafenib, lenvatinib, and radioactive iodine prior to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, a patient having a colorectal cancer (e.g., a RET-fusion positive colorectal cancer) has received treatment with a fluoropyrimidine-based chemotherapy, with or without anti-VEGF-directed therapy or anti-EGFR-directed therapy, prior to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, a patient having a pancreatic cancer (e.g., a RET-fusion positive pancreatic cancer) has received treatment with one or more of a fluoropyrimidine-based chemotherapy, a gemcitabine-based chemotherapy, and a S-1 chemotherapy prior to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, a patient having a breast cancer (e.g., a RET-fusion positive breast cancer) has received treatment with one or more of anthracycline, taxane, HER2-directed therapy, and hormonal therapy prior to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, a patient having a MTC (e.g., a RET-fusion positive MTC cancer) has received treatment with one or more of caboxantinib and vandetanib prior to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00342] In some embodiments of any the methods described herein, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered in combination with a therapeutically effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic) agents.

[00343] Non-limiting examples of additional therapeutic agents include: other RET-targeted therapeutic agents (i.e. a first or second RET kinase inhibitor), other kinase inhibitors (e.g., receptor tyrosine kinase-targeted therapeutic agents (e.g., Trk inhibitors or EGFR inhibitors)), signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g.

obataclax); cytotoxic chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents, including immunotherapy, and radiotherapy.

[00344] In some embodiments, the other RET-targeted therapeutic is a multikinase inhibitor exhibiting RET inhibition activity. In some embodiments, the other RET-targeted therapeutic inhibitor is selective for a RET kinase. Exemplary RET kinase inhibitors can exhibit inhibition activity (IC₅₀) against a RET kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a RET kinase inhibitors can exhibit inhibition activity (IC₅₀) against a RET kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

[00345] Non-limiting examples of RET-targeted therapeutic agents (e.g., a first RET inhibitor or a second RET inhibitor) include alectinib (9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile); amuvatinib (MP470, HPK56) (N-(1,3-benzodioxol-5-ylmethyl)-4-([1]benzofuro[3,2-d]pyrimidin-4-yl)piperazine-1-carbothioamide); apatinib (YN968D1) (N-[4-(1-cyanocyclopentyl) phenyl-2-(4-picolyl)amino-3-Nicotinamide methanesulphonate); cabozantinib (Cometriq XI.-184) (N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); dovitinib (TKI258; GFKI-258; CHIR-258) ((3Z)-4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1,3-dihydrobenzimidazol-2-ylidene]quinolin-2-one); famitinib (5-[2-(diethylamino)ethyl]-2-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-3-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4-one); fedratinib (SAR302503, TG101348) (N-(2-Methyl-2-propanyl)-3-{[5-methyl-2-({4-[2-(1-pyrrolidinyl)ethoxy]phenyl}amino)-4-pyrimidinyl]amino}benzenesulfonamide); foretinib (XL880, EXEL-2880, GSK1363089, GSK089) (N1'-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-N1-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); fostamantinib (R788) (2H-Pyrido[3,2-b]-1,4-oxazin-3(4H)-one, 6-[[5-fluoro-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinyl]amino]-2,2-dimethyl-4-[(phosphonoxy)methyl]-, sodium salt (1:2)); ilorasertib (ABT-348) (1-(4-(4-amino-7-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-3-yl)phenyl)-3-(3-fluorophenyl)urea); lenvatinib (E7080, Lenvima) (4-[3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy]-7-methoxy-6-quinolinecarboxamide); motesanib

(AMG 706) (N-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)amino]pyridine-3-carboxamide); nintedanib (3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone); ponatinib (AP24534) (3-(2-Imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]benzamide); PP242 (torkinib) (2-[4-Amino-1-(1-methylethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-1H-indol-5-ol); quizartinib (1-(5-(tert-Butyl)isoxazol-3-yl)-3-(4-(7-(2-morpholinoethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)urea); regorfenib (BAY 73-4506, stivarga) (4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate); RXDX-105 (CEP-32496, agerafenib) (1-(3-((6,7-dimethoxyquinazolin-4-yl)oxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea); semaxanib (SU5416) ((3Z)-3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-1,3-dihydro-2H-indol-2-one); sitravatinib (MGCD516, MG516) (N-(3-Fluoro-4-{[2-(5-{[(2-methoxyethyl)amino]methyl}-2-pyridinyl)thieno[3,2-b]pyridin-7-yl]oxy}phenyl)-N-(4-fluorophenyl)-1,1-cyclopropanedicarboxamide); sorafenib (BAY 43-9006) (4-[4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide); vandetanib (N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine); vatalanib (PTK787, PTK/ZK, ZK222584) (N-(4-chlorophenyl)-4-(pyridin-4-ylmethyl)phthalazin-1-amine); AD-57 (N-[4-[4-amino-1-(1-methylethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl]-N'-[3-(trifluoromethyl)phenyl]-urea); AD-80 (1-[4-(4-amino-1-propan-2-ylpyrazolo[3,4-d]pyrimidin-3-yl)phenyl]-3-[2-fluoro-5-(trifluoromethyl)phenyl]urea); AD-81 (1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(4-chloro-3-(trifluoromethyl)phenyl)urea); ALW-II-41-27 (N-(5-((4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbonyl)-2-methylphenyl)-5-(thiophen-2-yl)nicotinamide); BPR1K871 (1-(3-chlorophenyl)-3-(5-(2-((7-(3-(dimethylamino)propoxy)quinazolin-4-yl)amino)ethyl)thiazol-2-yl)urea); CLM3 (1-phenethyl-N-(1-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine); EBI-907 (N-(2-chloro-3-(1-cyclopropyl-8-methoxy-3H-pyrazolo[3,4-c]isoquinolin-7-yl)-4-fluorophenyl)-3-fluoropropane-1-sulfonamide); NVP-AST-487 (N-[4-[(4-ethyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-N'-[4-[[6-(methylamino)-4-pyrimidinyl]oxy]phenyl]-urea); NVP-BBT594 (BBT594) (5-((6-acetamidopyrimidin-4-yl)oxy)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-

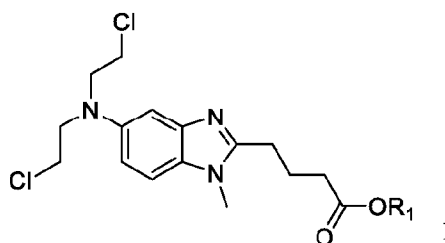
(trifluoromethyl)phenyl)indoline-1-carboxamide); PD173955 (6-(2,6-dichlorophenyl)-8-methyl-2-(3-methylsulfanylanilino)pyrido[2,3-d]pyrimidin-7-one); PP2 (4-amino-5-(4-chlorophenyl)-7-(dimethylethyl)pyrazolo[3,4-d]pyrimidine); PZ-1 (N-(5-(tert-butyl)isoxazol-3-yl)-2-(4-(5-(1-methyl-1H-pyrazol-4-yl)-1Hbenzo[d]imidazol-1-yl)phenyl)acetamide); RPI-1 (1,3-dihydro-5,6-dimethoxy-3-[(4-hydroxyphenyl)methylene]-H-indol-2-one; (3E)-3-[(4-hydroxyphenyl)methylidene]-5,6-dimethoxy-1H-indol-2-one); SGI-7079 (3-[2-[[3-fluoro-4-(4-methyl-1-piperazinyl)phenyl]amino]-5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-benzeneacetonitrile); SPP86 (1-Isopropyl-3-(phenylethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine); SU4984 (4-[4-[(E)-(2-oxo-1H-indol-3-ylidene)methyl]phenyl]piperazine-1-carbaldehyde); sunitinb (SU11248) (N-(2-Diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide); TG101209 (N-tert-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide); Withaferin A ((4 β ,5 β ,6 β ,22R)-4,27-Dihydroxy-5,6:22,26-diepoxyergosta-2,24-diene-1,26-dione); XL-999 ((Z)-5-((1-ethylpiperidin-4-yl)amino)-3-((3-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methylene)indolin-2-one); BPR1J373 (a 5-phenylthiazol-2-ylamine-pyrimidine derivative); CG-806 (CG'806); DCC-2157; GTX-186; HG-6-63-01 ((E)-3-(2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)vinyl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide); SW-01 (Cyclobenzaprine hydrochloride); XMD15-44 (N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(pyridin-3-ylethynyl)benzamide (generated from structure)); Y078-DM1 (an antibody drug conjugate composed of a RET antibody (Y078) linked to a derivative of the cytotoxic agent maytansine); Y078-DM4 (an antibody drug conjugate composed of a RET antibody (Y078) linked to a derivative of the cytotoxic agent maytansine); ITRI-305 (D0N5TB, DIB003599); BLU-667 (((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide); BLU6864; DS-5010; GSK3179106; GSK3352589; NMS-E668; and TAS0286/HM05.

[00346] Further examples of RET-targeted therapeutics (e.g., a first RET kinase inhibitor and a second RET kinase inhibitor) include 5-amino-3-(5-cyclopropylisoxazol-3-yl)-1-isopropyl-1H-pyrazole-4-carboxamide; 3-(5-cyclopropylisoxazol-3-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine; 3-((6,7-Dimethoxyquinazolin-4-yl)amino)-4-fluoro-2-methylphenol; N-(5-(tert-butyl)isoxazol-3-yl)-2-(4-(imidazo[1,2-a]pyridin-6-yl)phenyl)acetamide; N-(5-(tert-

butyl)isoxazol-3-yl)-2-(3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl)acetamide; N-(2-fluoro-5-trifluoromethylphenyl)-N'-{4'-[(2"-benzamido)pyridin-4"-ylamino]phenyl}urea; 2-amino-6-{[2-(4-chlorophenyl)-2-oxoethyl]sulfanyl}-4-(3-thienyl)pyridine-3,5-dicarbonitrile; and 3-aryllureidobenzylidene-indolin-2-ones.

[00347] Additional examples of other RET kinase inhibitors include those described in U.S. Patent Nos. 9,150,517 and 9,149,464, and International Publication No. WO 2014075035.

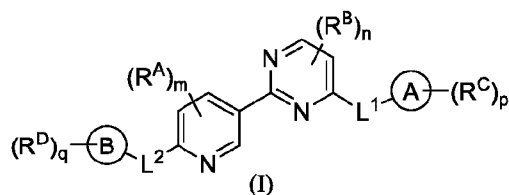
For example, in some embodiments the other RET inhibitor is a compound of formula I:



wherein R₁ is C₆-C₂₄alkyl or polyethylene glycol; or a pharmaceutically acceptable salt form thereof. In some embodiments, the other RET inhibitor is 4-{5-[bis-(chloroethyl)-amino]-1-methyl-1H-benzimidazol-2-yl}butyric acid dodecyl ester.

[00348] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO 2016127074.

For example, in some embodiments, the other RET inhibitor is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:



wherein Rings A and B are each independently selected from aryl, heteroaryl, cycloalkyl and heterocyclyl;

each L¹ and L² is independently selected from a bond, -(C1-C6 alkylene)-, -(C2-C6alkenylene)-, -(C2-C6 alkynylene)-, -(C1-C6 haloalkylene)-, -(C1-C6 heteroalkylene)-, -C(O)-, -O-, -S-, -S(O), -S(O)₂-, -N(R¹)-, -O-(C1-C6 alkylene)-, -(C1-C6 alkylene)-O-, -N(R¹)-C(O)-, -C(O)N(R¹)-, -(C1-C6 alkylene)-N(R¹)-, -N(R¹)-(C1-C6 alkylene)-, -N(R¹)-C(O)-(C1-C6 alkylene)-, -(C1-C6 alkylene)-N(R¹)-C(O)-, -C(O)-N(R¹)-(C1-C6 alkylene)-, -(C1-C6 alkylene)-

C(O)-N(R¹)-, -N(R¹)-S(O)₂-, -S(O)₂-N(R¹)-, -N(R¹)-S(O)₂-(C1-C6 alkylene)-, and -S(O)₂-N(R¹)-(C1-C6 alkylene)-; wherein each alkylene, alkenylene, alkynylene, haloalkylene, and heteroalkylene is independently substituted with 0-5 occurrences of R¹;

each R^A and R^B is independently selected from C1-C6 alkyl, C1-C6 alkoxy, halo, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C1-C6 heteroalkyl, and -N(R¹)(R¹); wherein each alkyl, alkoxy, haloalkyl, hydroxyalkyl, and heteroalkyl is independently substituted with 0-5 occurrences of R^a;

each R^C and R^D is independently selected from C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 alkoxy, halo, C1-C6 heteroalkyl, C1-C6 haloalkyl, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, -C(O)R¹, -OC(O)R¹, -C(O)OR¹, -(C1-C6 alkylene)-C(O)R¹, -SR¹, -S(O)₂R¹, -S(O)₂-N(R¹)(R¹), -(C1-C6 alkylene)-S(O)₂R¹, -(C1-C6 alkylene)-S(O)₂-N(R¹)(R¹), -N(R¹)(R¹)-C(O)-N(R¹)(R¹)-N(R¹)-C(O)R¹, -N(R¹)-C(O)OR¹, -(C1-C6 alkylene)-N(R¹)-C(O)R¹, -N(R¹)S(O)₂R¹, and -P(O)(R¹)(R¹); wherein each of alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a; or 2 R^C or 2 R^D together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^a;

each R¹ is independently selected from hydrogen, hydroxyl, halo, thiol, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C1-C6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of alkyl, thioalkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b, or 2 R¹ together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b;

each R^a and R^b is independently C1-C6 alkyl, halo, hydroxyl, C1-C6 haloalkyl, C1-C6 heteroalkyl, C1-C6 hydroxyalkyl, C1-C6 alkoxy, cycloalkyl, heterocyclyl, or cyano, wherein each of alkyl, haloalkyl, heteroalkyl, hydroxyalkyl, alkoxy, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R¹;

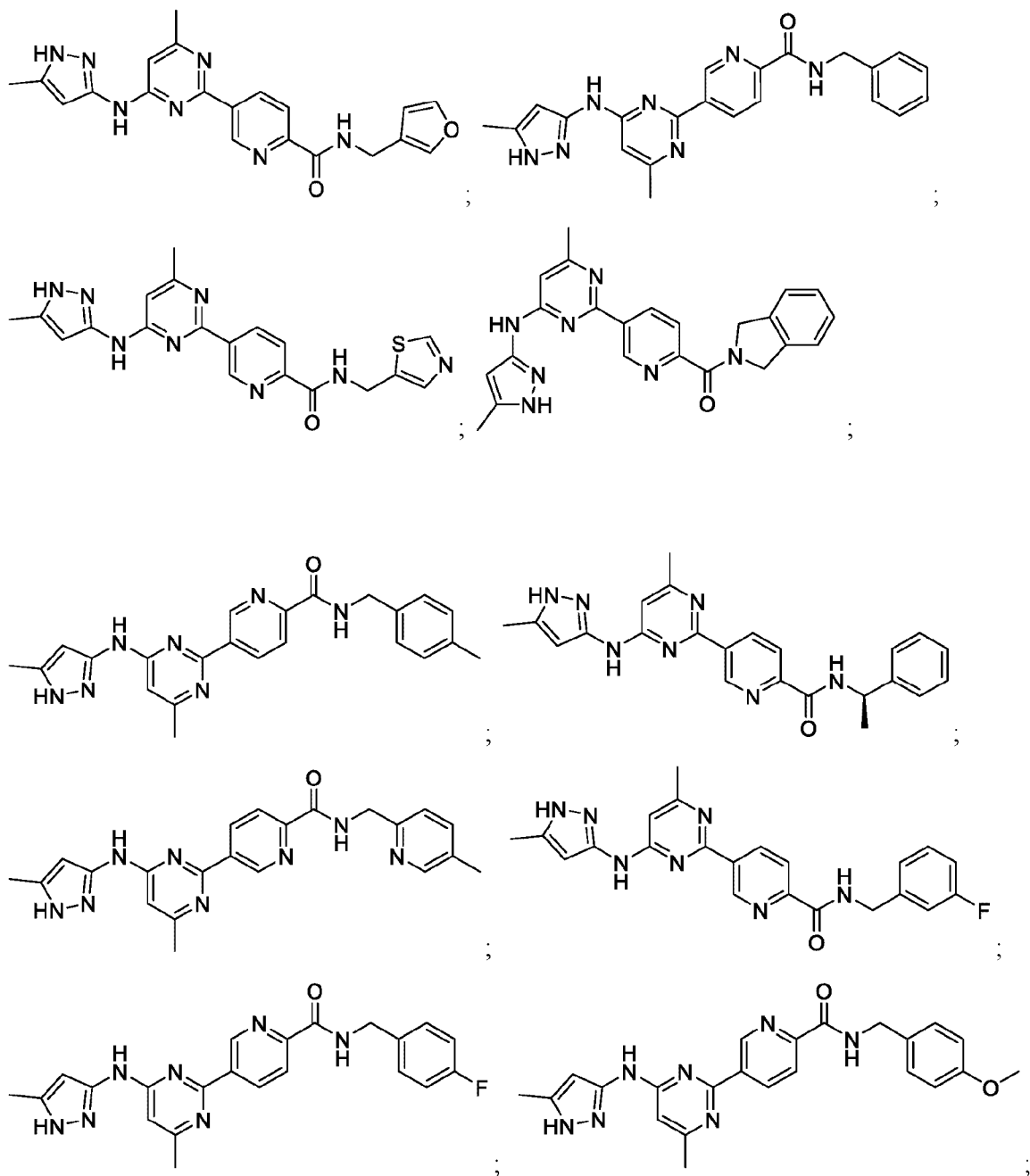
each R¹ is C1-C6 alkyl, C1-C6 heteroalkyl, halo, hydroxyl, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, cycloalkyl or cyano; or 2 R¹, together with the atom(s) to which they are attached

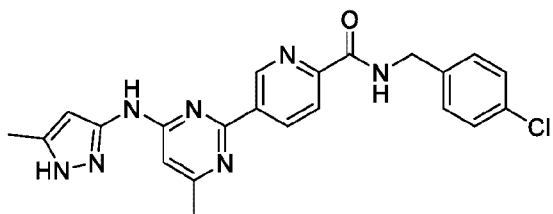
form a cycloalkyl or heterocyclyl ring;

m is 0, 1, 2, or 3;

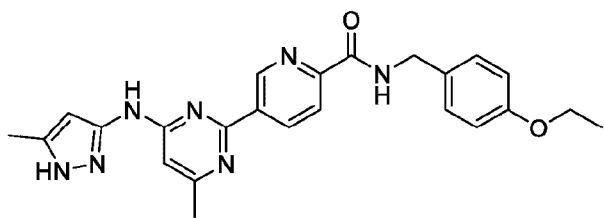
n is 0, 1, or 2; and

p and q are each independently 0, 1, 2, 3, or 4. For example, a RET inhibitor can be selected from the group consisting of:

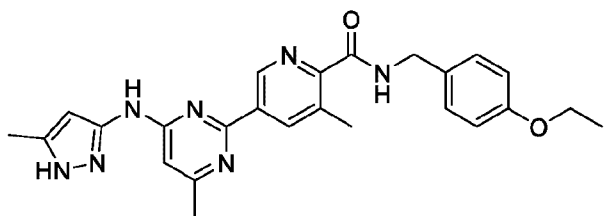




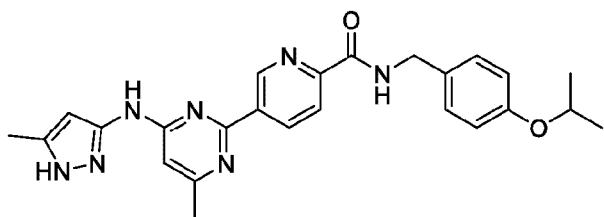
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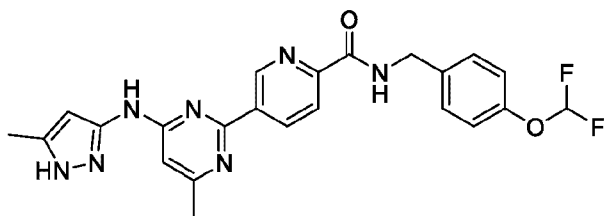
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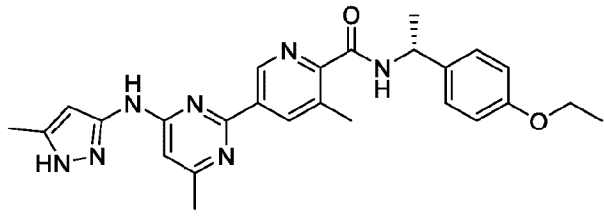
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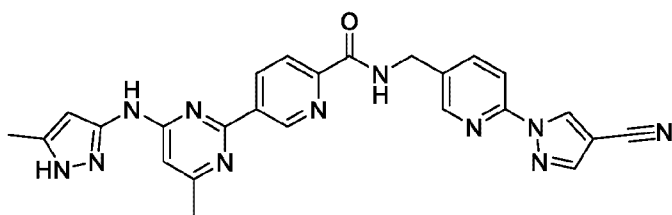
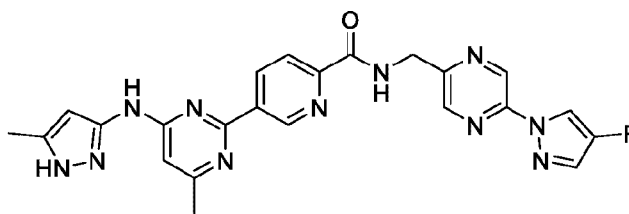
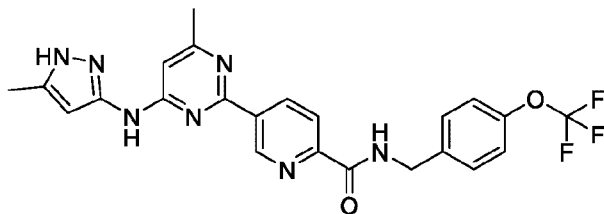
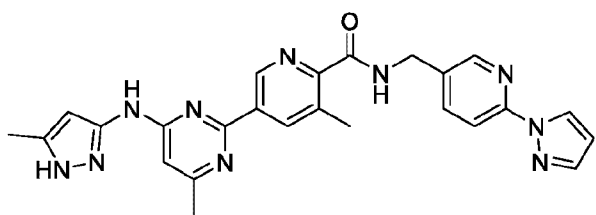
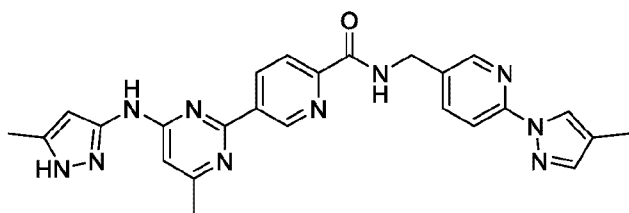
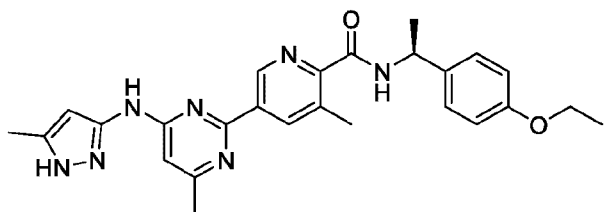
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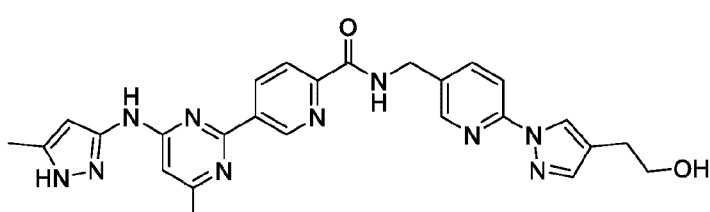
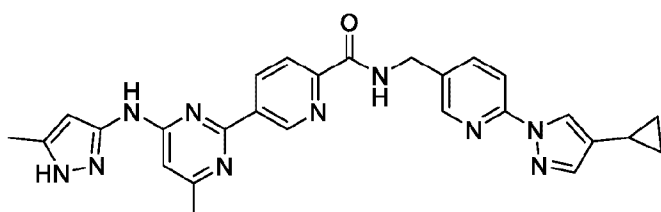
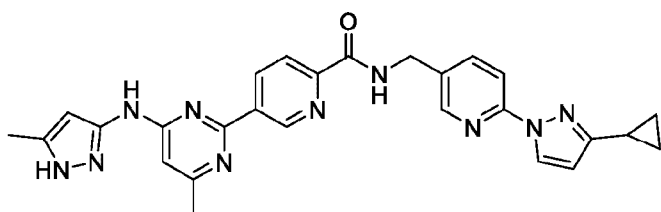
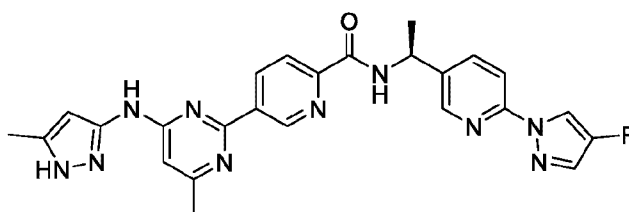
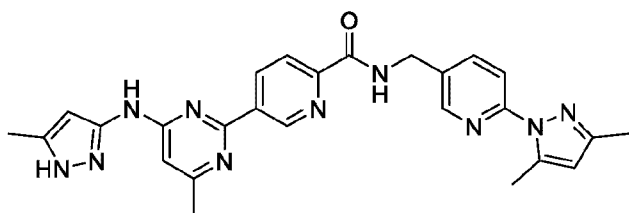
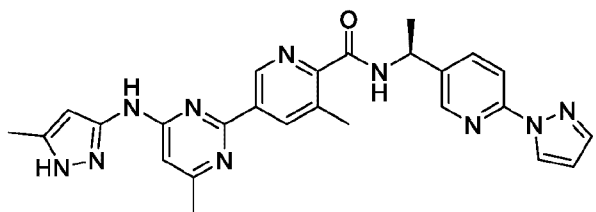


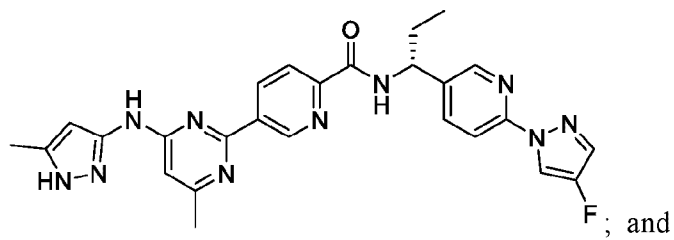
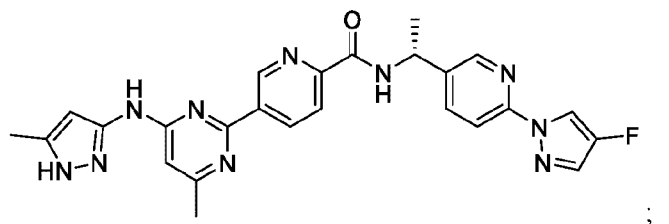
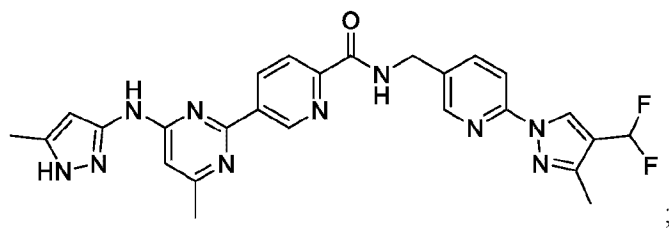
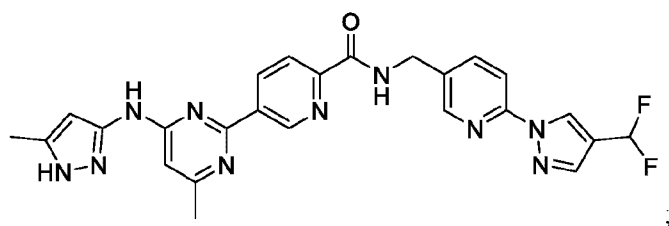
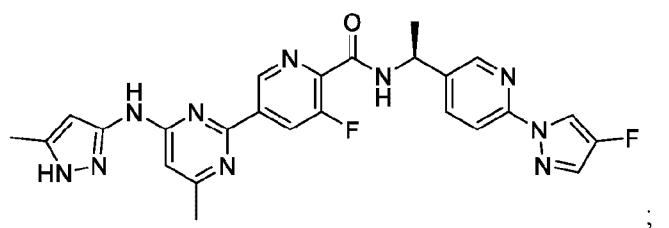
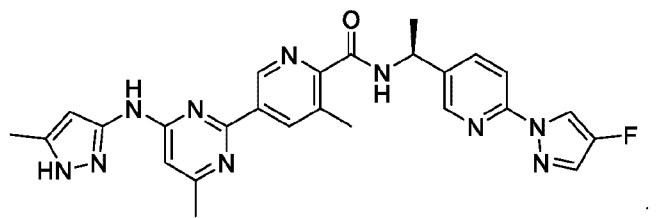
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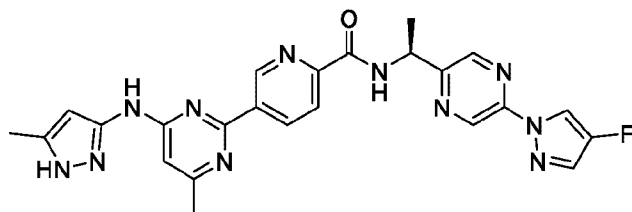


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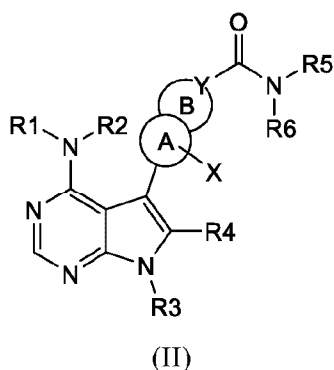


, or a pharmaceutically acceptable salt

thereof.

[00349] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO 2016075224.

For example, in some embodiments, the other RET inhibitor is a compound of Formula (II) or a pharmaceutically acceptable salt thereof, wherein:



R1 and R2 are independently hydrogen or an optionally substituted group selected from straight or branched (C₁-C₆) alkyl, (C₃-C₆) cycloalkyl and COR', wherein R' is an optionally substituted group selected from straight or branched (C₁-C₆) alkyl and (C₃-C₆) cycloalkyl;

R3 is hydrogen or an optionally substituted group selected from straight or branched (C₁-C₆) alkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₃-C₆) cycloalkyl, aryl, heteroaryl and a 3- to 7-membered heterocyclyl ring;

R4 is hydrogen or an optionally substituted group selected from straight or branched (C₁-C₆) alkyl, (C₂-C₆) alkenyl, aryl, heteroaryl or heterocyclyl;

A is a 5- or 6-membered heteroaryl ring or a phenyl ring;

B is a 5- or 6-membered ring selected from heteroaryl, (C₅-C₆) cycloalkyl and heterocyclyl ring or a phenyl ring; wherein ring A and ring B are fused together to form a bicyclic system comprising a 6-membered aromatic or 5- to 6-membered heteroaromatic ring fused with a 6-membered aromatic or 5- to 6-membered heteroaromatic, (C₅-C₆) cycloalkyl or heterocyclyl ring;

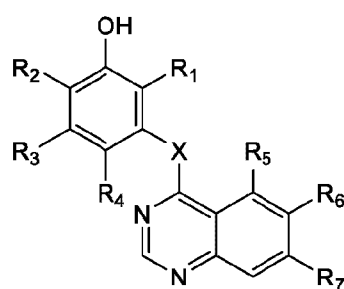
Y is carbon or nitrogen;

X is hydrogen, halogen, hydroxyl, cyano or an optionally substituted group selected from straight or branched (C₁-C₆) alkyl and (C₁-C₆) alkoxy; and

R₅ and R₆ are independently hydrogen or an optionally substituted group selected from straight or branched (C₁-C₆) alkyl, (C₃-C₆) cycloalkyl, heterocyclyl, aryl and heteroaryl.

[00350] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO 2015079251.

For example, in some embodiments, the other RET inhibitor is a compound of Formula (III) or a pharmaceutically acceptable salt or solvate thereof, wherein:



(III)

X is NH, NR_x, O or S, wherein R_x is (1-3C)alkyl;

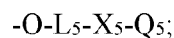
R₁ is selected from halo (e.g., fluoro, chloro, or bromo), trifluoromethyl, (1-4C)alkyl (e.g., methyl), (1-4C)alkoxy or (3-6C)cycloalkyl, wherein an alkyl, alkoxy or cycloalkyl group is optionally substituted with one or more fluoro;

R₂ is selected from hydrogen, halo (e.g., fluoro, chloro or bromo), hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl (e.g., methyl), (3-8C)cycloalkyl, or (1-4C)alkoxy (e.g., OMe), wherein an alkyl, cycloalkyl or alkoxy group is optionally substituted with one or more fluoro;

R₃ is selected from hydrogen, halo (e.g. fluoro, chloro or bromo), hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl (e.g., methyl), (3-8C)cycloalkyl, or (1-4C)alkoxy (e.g., OMe), wherein an alkyl, cycloalkyl or alkoxy group is optionally substituted with one or more fluoro;

R₄ is selected from hydrogen, halo (e.g., fluoro, chloro or bromo), hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl (e.g., methyl), (3-8C)cycloalkyl, or (1-4C)alkoxy (e.g., OMe), wherein an alkyl, cycloalkyl or alkoxy group is optionally substituted with one or more fluoro;

R₅ is selected from hydrogen or a group defined by the formula:



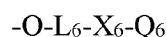
wherein

L₅ is absent or a linear or branched (1-4C)alkylene;

X₅ is absent or -C(O)O-, -O-, -C(O)-, -OC(O)-, -CH(QR_{5L})-, -N(R^J)-, -N(R_{5L})-C(O)-, -N(R_{5L})-C(O)O-, -C(O)-N(R_{5L})-, -S-, -SO-, -SO₂-, -S(O)₂N(R_{5L})-, or -N(R_{5L})SO₂- wherein R_{5L} is selected from hydrogen or methyl; and

Q₅ is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, aryl, aryl-(1-4C)alkyl, heteroaryl, heteroaryl-(1-4C)alkyl, heterocyclyl or heterocyclyl-(1-4C)alkyl;

R₆ is selected from hydrogen, or a group defined by the formula:



wherein

L₆ is absent or a linear or branched (1-4C)alkylene;

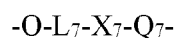
X₆ is absent or selected from -O-, -C(O)-, -C(O)O-, -OC(O)-, -CH(OR_{6L})-, -N(R_{6L}), -N(R_{6L})-C(O)-, -N(R_{6L})-C(O)O-, -C(O)-N(R_{6L})-, -S-, -SO-, -SO₂-, -S(O)₂N(R_{6L})-, or -N(R_{6L})SO₂- wherein R_{6L} is selected from hydrogen or (1-3C)alkyl;

Q₆ is hydrogen, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl, heterocyclyl-(1-6C)alkyl,

or Q₆ and R_{6L} are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring;

wherein R₆ is optionally substituted (e.g. substituted on L₆ and/or Q₆) with one or more (1-6C)alkyl, (1-6C)alkanoyl, OR_{6X}, SR_{6X}, S(O)R_{6X}, S(O)₂R_{6X}, C(O)OR_{6X} or C(O)NR_{6X}R'_{6X}, wherein R_{6X} and R'_{6X} are independently hydrogen, (1-8C)alkyl, or R_{6X} and R'_{6X} are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring; and

R₇ is selected from hydrogen, (1-6C)alkoxy, or a group defined by the formula:



wherein

L₇ is absent or a linear or branched (1-4C)alkylene;

X₇ is absent or selected from -O-, -C(O)-, -C(O)O-, -OC(O)-, -CH(OR_{6L})-, -N(R_{7L})-, -N(R_{7L})-C(O)-, -N(R_{7L})-C(O)O-, -C(O)-N(R_{7L})-, -S-, -SO-, -SO₂-, -S(O)₂N(R_{7L})-, or -N(R_{7L})SO₂- wherein R_{7L} is selected from hydrogen or (1-3C)alkyl;

Q₇ is hydrogen, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl, heterocyclyl-(1-6C)alkyl,

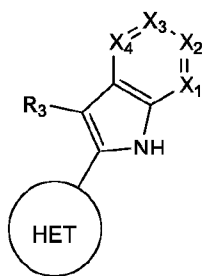
or Q₇ and R_{7L} are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring;

wherein R₇ is optionally substituted (e.g., substituted on L₇ and/or Q₇) with one or more halo, hydroxyl, nitro, cyano, (1-8C)alkyl, (1-8C)alkanoyl, OR_{7X}, SR_{7X}, S(O)R_{7X}, S(O)₂R_{7X}, C(O)OR_{7X} or C(O)NR_{7X}R'_{7X}, wherein R_{7X} and R'_{7X} are independently hydrogen, (1-8C)alkyl, or R_{7X} and R'_{7X} are linked such that, together with the nitrogen atom to which they are attached, they form a heterocyclic ring; or

R₇ is optionally substituted with one or more groups selected from oxo, (1-4C)haloalkyl, (1-4C)hydroxyalkyl, C(O)R_{7y} or NR_{7y}R'_{7y}, wherein R_{7y} and R'_{7y} are independently hydrogen or (1-8C)alkyl.

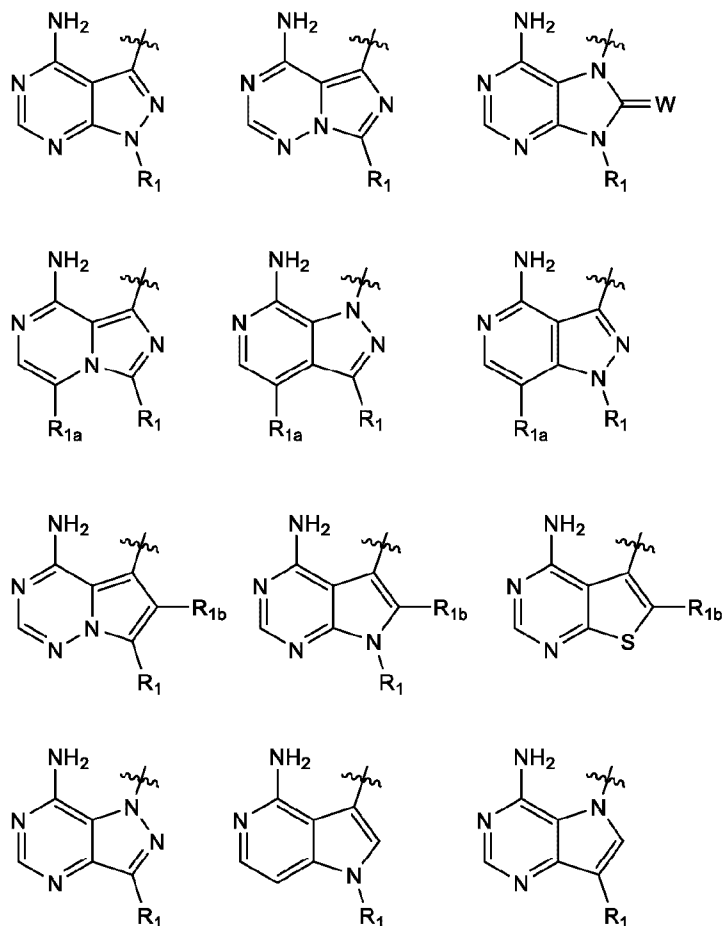
[00351] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO2017178845.

For example, in some embodiments, the other RET inhibitor is a compound of Formula (IV) or a pharmaceutically acceptable salt thereof, wherein:



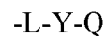
(IV)

HET is selected from one of the following:



wherein  denotes the point of attachment;

R₁ is selected from hydrogen, (1-4C)haloalkyl, (1-4C)haloalkoxy or a group of the formula:



wherein:

L is absent or (1-5C)alkylene optionally substituted by one or more substituents selected from (1-2C)alkyl or oxo;

Y is absent or O, S, SO, SO₂, N(R_a), C(O), C(O)O, OC(O), C(O)N(R_a), N(R_a)C(O), N(R_a)C(O)N(R_b), N(R_a)C(O)O, OC(O)N(R_a), S(O)₂N(R_a), or N(R_a)SO₂, wherein R_a and R_b are each independently selected from hydrogen or (1-4C)alkyl; and

Q is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, heteroaryl or heterocyclyl; wherein Q is optionally further substituted by one or more substituent groups independently selected from (1-4C)alkyl,

halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, amino, (1-4C)aminoalkyl, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, mercapto, ureido, NR_cR_d , OR_c , C(O)R_c , C(O)OR_c , OC(O)R_c , $\text{C(O)N(R}_d\text{)R}_c$, $\text{N(R}_d\text{)C(O)R}_c$, $\text{S(O)}_p\text{R}_c$ (where p is 0, 1 or 2), $\text{SO}_2\text{N(R}_d\text{)R}_c$, $\text{N(R}_d\text{)SO}_2\text{R}_c$, $\text{Si(R}_e\text{)(R}_d\text{)R}_c$ or $(\text{CH}_2)_q\text{NR}_c\text{R}_d$ (where q is 1, 2 or 3); wherein R_c , R_d and R_e are each independently selected from hydrogen, (1-6C)alkyl or (3-6C)cycloalkyl; or R_c and R_d are linked such that, together with the nitrogen atom to which they are attached, they form a 4-7 membered heterocyclic ring which is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano or hydroxy; or

Q is optionally substituted by a group of the formula:



wherein:

L_1 is absent or (1-3C)alkylene optionally substituted by one or more substituents selected from (1-2C)alkyl or oxo;

L_{Q1} is absent or selected from O, S, SO, SO_2 , $\text{N(R}_f\text{)}$, C(O) , C(O)O , OC(O) , $\text{C(O)N(R}_f\text{)}$, $\text{N(R}_f\text{)C(O)}$, $\text{N(R}_f\text{)C(O)N(R}_g\text{)}$, $\text{N(R}_f\text{)C(O)O}$, $\text{OC(O)N(R}_f\text{)}$, $\text{S(O)}_2\text{N(R}_f\text{)}$, or $\text{N(R}_f\text{)SO}_2$, wherein R_f and R_g are each independently selected from hydrogen or (1-2C)alkyl; and

W_1 is hydrogen, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl; wherein W_1 is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, mercapto, ureido, aryl, heteroaryl, heterocyclyl, (3-6C)cycloalkyl, NR_hR_i , OR_h , C(O)R_h , C(O)OR_h , OC(O)R_h , $\text{C(O)N(R}_i\text{)R}_h$, $\text{N(R}_i\text{)C(O)R}_h$, $\text{S(O)}_r\text{R}_h$ (where r is 0, 1 or 2), $\text{SO}_2\text{N(R}_i\text{)R}_h$, $\text{N(R}_i\text{)SO}_2\text{R}_h$ or $(\text{CH}_2)_s\text{NR}_i\text{R}_h$ (where s is 1, 2 or 3); wherein R_h and R_i are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl;

R_{1a} and R_{1b} are each selected from H, (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl or mercapto;

W is selected from O, S or NR_{W1} , wherein R_{W1} is selected from H or (1-2C)alkyl;

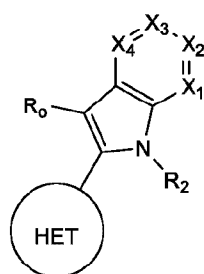
X₁, X₂, X₃ and X₄ are independently selected from CH, CR₂ or N;

R₂ is selected from hydrogen, halo, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)haloalkyl, (1-4C)haloalkoxy, amino, cyano, nitro, aryl, heteroaryl, heterocyclyl, cycloalkyl, (2-4C)alkynyl, NR_jR_k, OR_j, C(O)R_j, C(O)OR_j, OC(O)R_j, C(O)N(R_k)R_j, N(R_k)C(O)R_j, N(R_k)C(O)N(R_j), S(O)_{r1}R_k (where r₁ is 0, 1 or 2), SO₂N(R_j)R_k, N(R_j)SO₂R_k or (CH₂)_vNR_jR_k (where v is 1, 2 or 3); wherein R_j and R_k are each independently selected from hydrogen or (1-4C)alkyl; and wherein said (1-4C)alkyl, aryl, heteroaryl, heterocyclyl or cycloalkyl is optionally substituted by one or more substituents selected from halo, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)haloalkyl, (1-4C)haloalkoxy, amino, cyano, nitro, phenyl, (2-4C)alkynyl, NR_{j1}R_{k1}, OR_{j1}, C(O)R_{j1}, C(O)OR_{j1}, OC(O)R_{j1}, C(O)N(R_{k1})R_{j1}, N(R_{k1})C(O)R_{j1}, S(O)_{r2}R_{k1} (where r₂ is 0, 1 or 2), SO₂N(R_{j1})R_{k1}, N(R_{j1})SO₂R_{k1} or (CH₂)_{v1}NR_{j1}R_{k1} (where v₁ is 1, 2 or 3); and wherein R_{j1} and R_{k1} are each independently selected from hydrogen or (1-4C)alkyl; and

R₃ is selected from halo, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)haloalkyl, (1-4C)haloalkoxy, amino, cyano, nitro, (2-4C)alkynyl, NR_iR_m, OR_i, C(O)R_i, C(O)OR_i, OC(O)R_i, C(O)N(R_m)R_i, N(R_m)C(O)R_i, or (CH₂)_yNR_iR_m (where y is 1, 2 or 3); wherein said (1-4C)alkyl is optionally substituted by one or more substituents selected from amino, hydroxy, (1-2C)alkoxy or halo; and wherein R_i and R_m are each independently selected from hydrogen or (1-4C)alkyl.

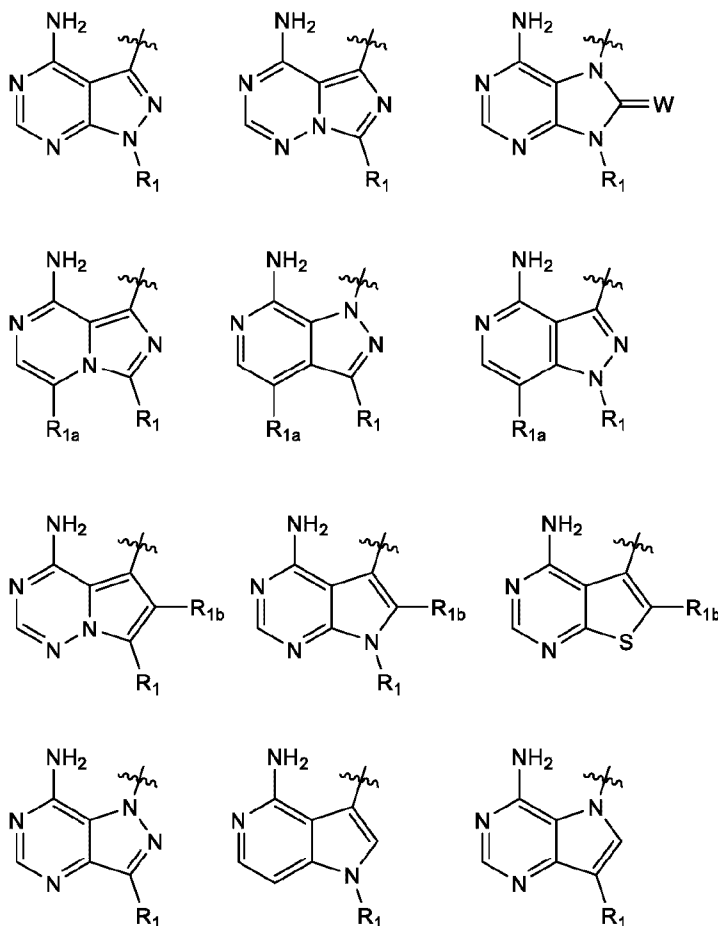
[00352] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO2017178844.

For example, in some embodiments, the other RET inhibitor is a compound of Formula (V) or a pharmaceutically acceptable salt thereof, wherein:



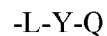
(V)

HET is selected from one of the following:



wherein  denotes the point of attachment;

R_1 is selected from hydrogen, (1-4C)haloalkyl, (1-4C)haloalkoxy or a group of the formula:



wherein:

L is absent or (1-5C)alkylene optionally substituted by one or more substituents selected from (1-2C)alkyl or oxo;

Y is absent or O, S, SO, SO_2 , $\text{N}(\text{R}_a)$, $\text{C}(\text{O})$, $\text{C}(\text{O})\text{O}$, $\text{OC}(\text{O})$, $\text{C}(\text{O})\text{N}(\text{R}_a)$, $\text{N}(\text{R}_a)\text{C}(\text{O})$, $\text{N}(\text{R}_a)\text{C}(\text{O})\text{N}(\text{R}_b)$, $\text{N}(\text{R}_a)\text{C}(\text{O})\text{O}$, $\text{OC}(\text{O})\text{N}(\text{R}_a)$, $\text{S}(\text{O})_2\text{N}(\text{R}_a)$, or $\text{N}(\text{R}_a)\text{SO}_2$, wherein R_a and R_b are each independently selected from hydrogen or (1-4C)alkyl; and

Q is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, aryl, (3-10C)cycloalkyl, (3-10C)cycloalkenyl, heteroaryl or heterocyclyl; wherein Q is optionally further substituted by one or more substituent groups independently selected from (1-4C)alkyl,

halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, amino, (1-4C)aminoalkyl, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, mercapto, ureido, NR_cR_d , OR_c , C(O)R_c , C(O)OR_c , OC(O)R_c , $\text{C(O)N(R}_d\text{)R}_c$, $\text{N(R}_d\text{)C(O)R}_c$, $\text{S(O)}_y\text{R}_c$ (where y is 0, 1 or 2), $\text{SO}_2\text{N(R}_d\text{)R}_c$, $\text{N(R}_d\text{)SO}_2\text{R}_c$, $\text{Si(R}_d\text{)(R}_c\text{)R}_e$ or $(\text{CH}_2)_z\text{NR}_c\text{R}_d$ (where z is 1, 2 or 3); wherein R_c , R_d and R_e are each independently selected from hydrogen, (1-6C)alkyl or (3-6C)cycloalkyl; or R_c and R_d can be linked such that, together with the nitrogen atom to which they are attached, they form a 4-7 membered heterocyclic ring which is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano or hydroxyl; or

Q is optionally substituted by a group of the formula:



wherein:

L_1 is absent or (1-3C)alkylene optionally substituted by one or more substituents selected from (1-2C)alkyl or oxo;

L_{Q1} is absent or selected from O, S, SO, SO_2 , $\text{N(R}_f\text{)}$, C(O) , C(O)O , OC(O) , $\text{C(O)N(R}_f\text{)}$, $\text{N(R}_f\text{)C(O)}$, $\text{N(R}_g\text{)C(O)N(R}_f\text{)}$, $\text{N(R}_f\text{)C(O)O}$, $\text{OC(O)N(R}_f\text{)}$, $\text{S(O)}_2\text{N(R}_f\text{)}$, or $\text{N(R}_f\text{)SO}_2$, wherein R_f and R_g are each independently selected from hydrogen or (1-2C)alkyl; and

Z_1 is hydrogen, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl; wherein Z_1 is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, mercapto, ureido, aryl, heteroaryl, heterocycyl, (3-6C)cycloalkyl, NR_hR_i , OR_h , C(O)R_h , C(O)OR_h , OC(O)R_h , $\text{C(O)N(R}_i\text{)R}_h$, $\text{N(R}_i\text{)C(O)R}_h$, $\text{S(O)}_{y^a}\text{R}_h$ (where y^a is 0, 1 or 2), $\text{SO}_2\text{N(R}_i\text{)R}_h$, $\text{N(R}_i\text{)SO}_2\text{R}_h$ or $(\text{CH}_2)_{z^a}\text{NR}_i\text{R}_h$ (where z^a is 1, 2 or 3); wherein R_h and R_i are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl;

R_{1a} and R_{1b} are each selected from hydrogen, (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl or mercapto;

W is selected from O, S or NR_j , wherein R_j is selected from H or (1-2C)alkyl;

X₁ and X₂ are each independently selected from N or CR_k;

wherein

R_k is selected from hydrogen, halo, (1-4C)alkyl, (1-4C)alkoxy, amino, (1-4C)alkylamino, (1-4C)dialkylamino, cyano, (2C)alkynyl, C(O)R_{k1}, C(O)OR_{k1}, OC(O)R_{k1}, C(O)N(R_{k2})R_{k1}, N(R_{k2})C(O)R_{k1}, S(O)_{y^b}R_{k1} (where y^b is 0, 1 or 2), SO₂N(R_{k2})R_{k1}, N(R_{k2})SO₂R_{k1} or (CH₂)_{z^b}NR_{k1}R_{k2} (where z^b is 1, 2 or 3); wherein said (1-4C)alkyl is optionally substituted by one or more substituents selected from amino, hydroxy, (1-2C)alkoxy or halo; and

R_{k1} and R_{k2} are each independently selected from hydrogen or (1-4C)alkyl;

X₃ is selected from N or CR_m;

wherein

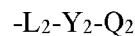
R_m is selected from hydrogen, halo, (1-4C)alkyl, (1-4C)alkoxy, amino, (1-4C)alkylamino, (1-4C)dialkylamino, cyano, (2C)alkynyl, C(O)R_{m1}, C(O)OR_{m1}, OC(O)R_{m1}, C(O)N(R_{m2})R_{m1}, N(R_{m2})C(O)R_{m1}, S(O)_{y^c}R_{m1} (where y^c is 0, 1 or 2), SO₂N(R_{m2})R_{m1}, N(R_{m2})SO₂R_{m1} or (CH₂)_{z^c}NR_{m1}R_{m2} (where z^c is 1, 2 or 3); wherein said (1-4C)alkyl is optionally substituted by one or more substituents selected from amino, hydroxy, (1-2C)alkoxy or halo; and

R_{m1} and R_{m2} are each independently selected from hydrogen or (1-4C)alkyl;

R_o is selected from halo, (1-4C)alkyl, (1-4C)alkoxy, amino, (1-4C)alkylamino, (1-4C)dialkylamino, cyano, (2C)alkynyl, C(O)R_{o1}, C(O)OR_{o1}, OC(O)R_{o1}, C(O)N(R_{o2})R_{o1}, N(R_{o2})C(O)R_{o1}, S(O)_{y^d}R_{o1} (where y^d is 0, 1 or 2), SO₂N(R_{o2})R_{o1}, N(R_{o2})SO₂R_{o1} or (CH₂)_{z^d}NR_{o1}R_{o2} (where z^d is 1, 2 or 3); wherein said (1-4C)alkyl is optionally substituted by one or more substituents selected from amino, hydroxy, (1-2C)alkoxy or halo; and

R_{o1} and R_{o2} are each independently selected from hydrogen or (1-4C)alkyl;

R₂ is selected from hydrogen, (1-4C)alkyl or a group of the formula:



wherein:

L₂ is absent or (1-3C)alkylene optionally substituted by one or more substituents selected from (1-2C)alkyl or oxo;

Y₂ is absent or C(O), C(O)O, C(O)N(R_p), wherein R_p is selected from hydrogen or (1-4C)alkyl; and

Q₂ is hydrogen, (1-6C)alkyl, aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl; wherein Q₂ is optionally further substituted by one or more substituent groups independently selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, amino, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, NR_qR_r, OR_q, wherein R_q and R_r are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl;

R₃ is selected from a group of the formula:



wherein:

Y₃ is C(O), C(O)N(R_y), C(O)N(R_y)O, N(R_y)(O)C, C(O)O, OC(O), N(R_y)C(O)N(R_{y1}), SO₂N(R_y), N(R_y)SO₂, oxazolyl, triazolyl, oxadiazolyl, thiazolyl, imidazolyl, thiadiazolyl, pyridinyl, pyrazolyl, pyrrolyl or tetrazolyl, wherein R_y and R_{y1} are independently selected from hydrogen or (1-2C)alkyl; and

Q₃ is hydrogen, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl; wherein Q₃ is optionally further substituted by one or more substituent groups independently selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, amino, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, NR_zR_{aa}, OR_z, wherein R_z and R_{aa} are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl; or Q₃ is optionally substituted by a group of the formula:



wherein:

L₄ is absent or (1-3C)alkylene optionally substituted by one or more substituents selected from (1-2C)alkyl or oxo;

L_{Q4} is absent or selected from O, S, SO, SO₂, N(R_{ab}), C(O), C(O)O, OC(O), C(O)N(R_{ab}), N(R_{ab})C(O), N(R_{ac})C(O)N(R_{ab}), N(R_{ab})C(O)O, OC(O)N(R_{ab}), S(O)₂N(R_{ab}), or N(R_{ab})SO₂, wherein R_{ab} and R_{ac} are each independently selected from hydrogen or (1-2C)alkyl; and

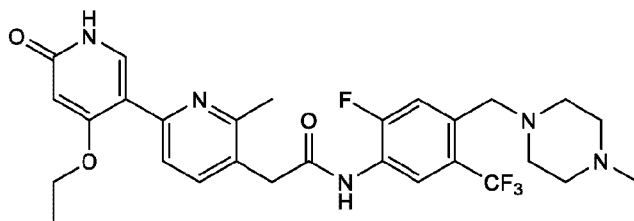
Z₄ is hydrogen, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl; wherein Z₄ is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano, hydroxy, carboxy, carbamoyl, sulphamoyl, mercapto, ureido, aryl, heteroaryl, heterocyclyl, (3-

6C)cycloalkyl, $\text{NR}_{\text{ad}}\text{R}_{\text{ae}}$, OR_{ad} , $\text{C(O)}\text{R}_{\text{ad}}$, $\text{C(O)}\text{OR}_{\text{ad}}$, $\text{OC(O)}\text{R}_{\text{ad}}$, $\text{C(O)}\text{N(R}_{\text{ae}})\text{R}_{\text{ad}}$, $\text{N(R}_{\text{ae}})\text{C(O)}\text{R}_{\text{ad}}$, $\text{S(O)}_{y^e}\text{R}_{\text{ad}}$ (where y^e is 0, 1 or 2), $\text{SO}_2\text{N(R}_{\text{ae}})\text{R}_{\text{ad}}$, $\text{N(R}_{\text{ae}})\text{SO}_2\text{R}_{\text{ad}}$ or $(\text{CH}_2)_{z^e}\text{NR}_{\text{ad}}\text{R}_{\text{ae}}$ (where z^e is 1, 2 or 3); wherein R_{ad} and R_{ae} are each independently selected from hydrogen, (1-4C)alkyl or (3-6C)cycloalkyl; or

Q_3 and R_y are linked such that, together with the nitrogen atom to which they are attached, they form a 4-7 membered heterocyclic ring which is optionally substituted by one or more substituents selected from (1-4C)alkyl, halo, (1-4C)haloalkyl, (1-4C)haloalkoxy, (1-4C)alkoxy, (1-4C)alkylamino, amino, cyano or hydroxyl;

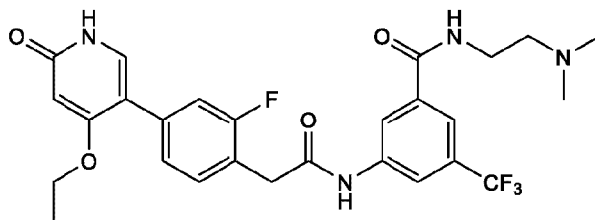
with the proviso that only one or two of X_1 , X_2 or X_3 can be N.

[00353] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO 2017145050. For example, in some embodiments, the other RET has the Formula (VI) or is a pharmaceutically acceptable salt thereof.

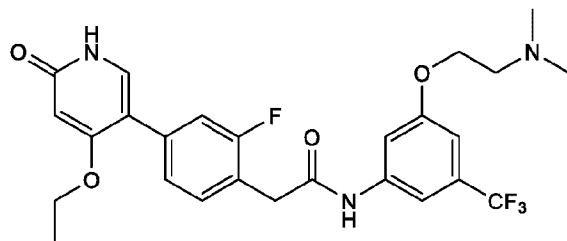


(VI)

[00354] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO 2016038552. For example, in some embodiments, the other RET has the Formula (VII), or the Formula (VIII), or is a pharmaceutically acceptable salt thereof.



(VII)

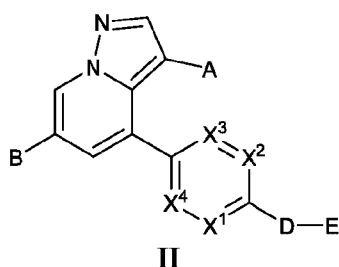


(VIII)

[00355] Yet other therapeutic agents include RET inhibitors such as those described, for example, in U.S. Patent Nos. 10,030,005; 9,738,660; 9,801,880; 9,682,083; 9,789,100; 9,550,772; 9,493,455; 9,758,508; 9,604,980; 9,321,772; 9,522,910; 9,669,028; 9,186,318; 8,933,230; 9,505,784; 8,754,209; 8,895,744; 8,629,135; 8,815,906; 8,354,526; 8,741,849; 8,461,161; 8,524,709; 8,129,374; 8,686,005; 9,006,256; 8,399,442; 7,795,273; 7,863,288; 7,465,726; 8,552,002; 8,067,434; 8,198,298; 8,106,069; 6,861,509; 8,299,057; 9,150,517; 9,149,464; 8,299,057; and 7,863,288; U.S. Publication Nos. 2018/0009818; 2018/0009817; 2017/0283404; 2017/0267661; 2017/0298074; 2017/0114032; 2016/0009709; 2015/0272958; 2015/0238477; 2015/0099721; 2014/0371219; 2014/0137274; 2013/0079343; 2012/0283261; 2012/0225057; 2012/0065233; 2013/0053370; 2012/0302567; 2011/0189167; 2016/0046636; 2013/0012703; 2011/0281841; 2011/0269739; 2012/0271048; 2012/0277424; 2011/0053934; 2011/0046370; 2010/0280012; 2012/0070410; 2010/0081675; 2010/0075916; 2011/0212053; 2009/0227556; 2009/0209496; 2009/0099167; 2010/0209488; 2009/0012045; 2013/0303518; 2008/0234267; 2008/0199426; 2010/0069395; 2009/0312321; 2010/0173954; 2011/0195072; 2010/0004239; 2007/0149523; 2017/0281632; 2017/0226100; 2017/0121312; 2017/0096425; 2017/0044106; 2015/0065468; 2009/0069360; 2008/0275054; 2007/0117800; 2008/0234284; 2008/0234276; 2009/0048249; 2010/0048540; 2008/0319005; 2009/0215761; 2008/0287427; 2006/0183900; 2005/0222171; 2005/0209195; 2008/0262021; 2008/0312192; 2009/0143399; 2009/0130229; 2007/0265274; 2004/0185547; and 2016/0176865; and International Publication Nos. WO 2018/149382; WO 2018/136796; WO 2017/079140; WO 2017/145050; WO 2017/097697; WO 2017/049462; WO 2017/043550; WO 2017/027883; WO 2017/013160; WO 2017/009644; WO 2016/168992; WO 2016/137060; WO 2016/127074; WO 2016/075224; WO 2016/038552; WO 2015/079251; WO 2014/086284; WO 2013/042137; WO 2013/036232; WO 2013/016720; WO 2012/053606; WO 2012/047017; WO 2007/109045; WO 2009/042646; WO 2009/023978; WO 2009/017838; WO 2017/178845; WO 2017/178844; WO 2017/146116; WO 2017/026718; WO

2016/096709; WO 2007/057397; WO 2007/057399; WO 2007/054357; WO 2006/130613; WO 2006/089298; WO 2005/070431; WO 2003/020698; WO 2001/062273; WO 2001/016169; WO 1997/044356; WO 2007/087245; WO 2005/044835; WO 2014/075035; and WO 2016/038519, and *J. Med.Chem.* 2012, 55 (10), 4872-4876.

[00356] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is a compound of the Formula **II**:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

X¹ is CH, CCH₃, CF, CCl or N;

X² is CH, CF or N;

X³ is CH, CF or N;

X⁴ is CH, CF or N;

wherein zero, one or two of X¹, X², X³ and X⁴ is N;

A is H, Cl, CN, Br, CH₃, CH₂CH₃ or cyclopropyl;

B is hetAr¹;

hetAr¹ is a 5-membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl, hydroxyC1-C6 alkyl, fluoroC1-C6 alkyl, difluoroC1-C6 alkyl, trifluoroC1-C6 alkyl, cyanoC1-C6 alkyl, (C1-C6 alkoxy)C1-C6 alkyl, (C1-C4 alkoxy)CH₂C(=O)-, (C1-C4 alkoxy)C(=O)C1-C3 alkyl, C3-C6 cycloalkyl, (R^aR^bN)C1-C6 alkyl, (R^aR^bN)C(=O)C1-C6 alkyl, (C1-C6 alkylSO₂)C1-C6 alkyl, hetCyc^a, and 4-methoxybenzyl;

R^a and R^b are independently H or C1-C6 alkyl;

hetCyc^a is a 4-6 membered heterocyclic ring having a ring heteroatom selected from N and O,

wherein said heterocyclic ring is optionally substituted with halogen, C1-C6 alkyl, fluoroC1-C6 alkyl, difluoroC1-C6 alkyl, trifluoroC1-C6 alkyl, (C1-C6 alkoxy)C1-C6 alkyl, di(C1-C3 alkyl)NCH₂C(=O), (C1-C6 alkoxy)C(=O) or (C1-C6 alkoxy)CH₂C(=O);

D is hetCyc¹, hetCyc², hetCyc³ or hetCyc⁹;

hetCyc¹ is a 4-6 membered heterocyclic ring having 1-2 ring atoms selected from N and O, wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from the group consisting of C1-C3 alkyl, fluoroC1-C3 alkyl, difluoroC1-C3 alkyl, trifluoroC1-C3 alkyl and OH, or said heterocyclic ring is substituted with a C3-C6 cycloalkylidene ring, or said heterocyclic ring is substituted with an oxo group;

hetCyc² is a 7-8 membered bridged heterocyclic ring having 1-3 ring heteroatoms independently selected from N and O, wherein said heterocyclic ring is optionally substituted with C1-C3 alkyl;

hetCyc³ is a 7-11 membered heterospirocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein said ring is optionally substituted with C1-C3 alkyl;

hetCyc⁹ is a fused 9-10 membered heterocyclic ring having 1-3 ring nitrogen atoms and optionally substituted with oxo;

E is

- (a) hydrogen,
- (b) OH,
- (c) R^aR^bN-, wherein R^a is H or C1-C6 alkyl and R^b is H, C1-C6 alkyl or phenyl;
- (d) C1-C6 alkyl optionally substituted with one to three fluoros,
- (e) hydroxyC1-C6 alkyl- optionally substituted with one to three fluoros,
- (f) C1-C6 alkoxy optionally substituted with one to three fluoros,
- (g) hydroxy(C1-C6 alkoxy) optionally substituted with one to three fluoros,
- (h) (C1-C6 alkoxy)hydroxy C1-C6 alkyl- optionally substituted with one to three fluoros,
- (i) (C1-C6 alkyl)C(=O)- optionally substituted with one to three fluoros,
- (j) (hydroxy C1-C6 alkyl)C(=O)- optionally substituted with one to three fluoros,
- (k) (C1-C6 alkoxy)C(=O)-,
- (l) (C1-C6 alkoxy)(C1-C6 alkyl)C(=O)-,
- (m) HC(=O)-,
- (n) Cyc¹,

- (o) $\text{Cyc}^1\text{C}(=\text{O})-$,
- (p) $\text{Cyc}^1(\text{C1-C6 alkyl})\text{C}(=\text{O})-$ wherein said alkyl portion is optionally substituted with one or more groups independently selected from the group consisting of OH, fluoro, C1-C3 alkoxy and $\text{R}^c\text{R}^d\text{N}-$, where R^c and R^d are independently H or C1-C6 alkyl,
- (q) hetCyc^4 ,
- (r) $\text{hetCyc}^4\text{C}(=\text{O})-$,
- (s) $\text{hetCyc}^4(\text{C1-C3 alkyl})\text{C}(=\text{O})-$,
- (t) $(\text{hetCyc}^4)\text{C}(=\text{O})\text{C1-C2 alkyl}-$,
- (u) $\text{hetCyc}^4\text{C}(=\text{O})\text{NH}-$,
- (v) Ar^2 ,
- (w) $\text{Ar}^2\text{C}(=\text{O})-$,
- (x) $\text{Ar}^2\text{C1-C6 alkyl}-$,
- (y) $(\text{Ar}^2)\text{hydroxy C2-C6 alkyl}-$,
- (z) $\text{Ar}^2(\text{C1-C3 alkyl})\text{C}(=\text{O})-$ wherein said alkyl portion is optionally substituted with one or two groups independently selected from the group consisting of OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, C1-C6 alkoxy and $\text{R}^e\text{R}^f\text{N}-$, where R^e and R^f are independently H or C1-C6 alkyl, or R^e and R^f together with the nitrogen to which they are attached form a 5-6 membered azacyclic ring optionally having an additional ring heteroatom selected from N and O,
- (aa) $\text{hetAr}^2\text{C}(=\text{O})-$,
- (bb) $(\text{hetAr}^2)\text{hydroxyC2-C6 alkyl}-$,
- (cc) $\text{hetAr}^2(\text{C1-C3 alkyl})\text{C}(=\text{O})-$, wherein said alkyl portion is optionally substituted with one or two groups independently selected from the group consisting of OH, C1-C6 alkyl, hydroxyC1-C6 alkyl, C1-C6 alkoxy and $\text{R}^e\text{R}^f\text{N}-$, wherein R^e and R^f are independently H or C1-C6 alkyl or R^e and R^f together with the nitrogen to which they are attached form a 5-6 membered azacyclic ring optionally having an additional ring heteroatom selected from N and O,
- (dd) $\text{R}^1\text{R}^2\text{NC}(=\text{O})-$,
- (ee) $\text{R}^1\text{R}^2\text{N}(\text{C1-C3 alkyl})\text{C}(=\text{O})-$, wherein said alkyl portion is optionally substituted with phenyl,
- (ff) $\text{R}^1\text{R}^2\text{NC}(=\text{O})\text{C1-C2 alkyl}-$,

- (gg) $R^1R^2NC(=O)NH-$,
- (hh) $CH_3SO_2(C1-C6 \text{ alkyl})C(=O)-$,
- (ii) $(C1-C6 \text{ alkyl})SO_2-$,
- (jj) $(C3-C6 \text{ cycloalkyl})CH_2SO_2-$,
- (kk) $hetCyc^5-SO_2-$,
- (ll) $R^4R^5NSO_2-$,
- (mm) $R^6C(=O)NH-$,
- (nn) $hetCyc^6$,
- (oo) $hetAr^2C1-C6 \text{ alkyl}-$,
- (pp) $(hetCyc^4)C1-C6 \text{ alkyl}-$,
- (qq) $(C1-C6 \text{ alkoxy})C1-C6 \text{ alkyl}-$ optionally substituted with 1-3 fluoros,
- (rr) $(C3-C6 \text{ cycloalkoxy})C1-C6 \text{ alkyl}-$,
- (ss) $(C3-C6 \text{ cycloalkyl})C1-C6 \text{ alkyl}-$, wherein said cycloalkyl is optionally substituted with 1-2 fluoros,
- (tt) $(R^gR^hN)C1-C6 \text{ alkyl}-$, wherein R^g and R^h are independently H or C1-C6 alkyl,
- (uu) Ar^2-O- ,
- (vv) $(C1-C6 \text{ alkyl}SO_2)C1-C6 \text{ alkyl}-$,
- (ww) $(C1-C6 \text{ alkoxy})C(=O)NHC1-C6 \text{ alkyl}-$,
- (xx) $(C3-C6 \text{ cycloalkoxy})C(=O)-$,
- (yy) $(C3-C6 \text{ cycloalkyl})SO_2-$, wherein said cycloalkyl is optionally substituted with C1-C6 alkyl,
- (zz) $Ar^4CH_2OC(=O)-$,
- (aaa) $(N-(C1-C3 \text{ alkyl})pyridinonyl)C1-C3 \text{ alkyl}-$, and
- (bbb) $(Ar^4SO_2)C1-C6 \text{ alkyl}-$;

Cyc^1 is a C3-C6 cycloalkyl, wherein (a) said cycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of OH, halogen, C1-C6 alkoxy, CN, hydroxyC1-C6 alkyl, (C1-C6 alkoxy)C1-C6 alkyl, and C1-C6 alkyl optionally substituted with 1-3 fluoros, or (b) said cycloalkyl is substituted with phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C3 alkyl, C1-C3 alkoxy and CF, or (c) said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N

and O, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C3 alkyl, C1-C3 alkoxy and CF₃;

Ar² is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl, C1-C6 alkoxy (optionally substituted with 1-3 fluoros), fluoroC1-C6 alkyl, difluoroC1-C6 alkyl, trifluoroC1-C6 alkyl, CN, a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, and RⁱR^jN- wherein Rⁱ and R^j are independently H or C1-C6 alkyl;

hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl, C1-C6 alkoxy (optionally substituted with 1-3 fluoros), fluoroC1-C6 alkyl, difluoroC1-C6 alkyl, trifluoroC1-C6 alkyl, hydroxyC1-C6 alkyl, (C3-C6)cycloalkyl, (C1-C6 alkoxy)C1-C6 alkyl, CN, OH, and R'R"N-, wherein R' and R" are independently H or C1-C3 alkyl;

hetCyc⁴ is (a) a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said S is optionally oxidized to SO₂, (b) a 7-8 membered bridged heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, (c) a 6-12 membered fused bicyclic heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally independently substituted with 1-2 C1-C6 alkyl substituents, or (d) a 7-10 membered spirocyclic heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein each of said heterocyclic rings is optionally substituted with one or more substituents independently selected from the group consisting of halogen, OH, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy, (C1-C6 alkoxy)C1-C6 alkyl, (C3-C6)cycloalkyl, (C1-C6 alkyl)C(=O)-, a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, and phenyl wherein said phenyl is optionally substituted with one or more substituents selected from halogen, C1-C6 alkyl and C1-C6 alkoxy;

hetCyc⁵ is a 5-6 membered heterocyclic ring having a ring heteroatom selected from O and N;

hetCyc⁶ is a 5 membered heterocyclic ring having one or two ring heteroatoms independently selected from N and O, wherein said ring is substituted with oxo and wherein said ring is further optionally substituted with one or more substituents independently selected from the group consisting of OH and C1-C6 alkyl;

R¹ is H, C1-C6 alkyl or (C1-C6 alkoxy)C1-C6 alkyl;

R^2 is H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl (optionally substituted with 1-3 fluoros), Cyc^3 , hydroxyC1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C(=O), $hetCyc^7$, Ar^3 , Ar^3C1-C3 alkyl-, hydroxyC1-C6 alkoxy or (3-6C cycloalkyl)CH₂O-;

Cyc^3 is a 3-6 membered carbocyclic ring optionally substituted with 1-2 groups independently selected from the group consisting of C1-C6 alkoxy, OH and halogen;

$hetCyc^7$ is a 5-6 membered heterocyclic ring having a ring heteroatom selected from O and N wherein said ring is optionally substituted with C1-C6 alkyl;

Ar^3 is phenyl optionally substituted with one or more substituents independently selected from halogen, C1-C3 alkyl, C1-C3 alkoxy, fluoroC1-C3 alkyl, difluoroC1-C3 alkyl and trifluoroC1-C3 alkyl;

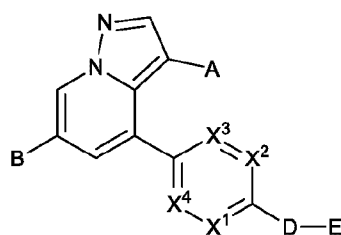
R^4 and R^5 are independently H or C1-C6 alkyl;

R^6 is C1-C6 alkyl, hydroxyC1-C6 alkyl, C1-C6 alkoxy, (C1-C6 alkoxy)C1-C6 alkyl, phenyl or $hetCyc^8$;

$hetCyc^8$ is a 5-6 membered heterocyclic ring having a ring heteroatom selected from O and N, wherein said heterocyclic ring is optionally substituted with C1-C6 alkyl; and

Ar^4 is phenyl optionally substituted with one or more halogens.

[00357] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is a compound of the Formula **III**:



III

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X^1 is CH or N;

X^2 is CH or N;

X^3 is CH or N;

X^4 is CH or N;

wherein one or two of X^1 , X^2 , X^3 and X^4 is N;

A is CN;

B is hetAr^1 ;

hetAr^1 is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl, hydroxyC1-C6 alkyl, fluoroC1-C6 alkyl, difluoroC1-C6 alkyl, trifluoroC1-C6 alkyl, cyanoC1-C6 alkyl, (C1-C6 alkoxy)C1-C6 alkyl, (C1-C4 alkoxy)CH₂C(=O)-, (C1-C4 alkoxy)C(=O)C1-C3 alkyl, C3-C6 cycloalkyl, ($R^a R^b$ N)C1-C6 alkyl, ($R^a R^b$ N)C(=O)C1-C6 alkyl, (C1-C6 alkylSO₂)C1-C6 alkyl, and 4-methoxybenzyl;

R^a and R^b are independently H or C1-C6 alkyl;

D is hetCyc^1 ;

hetCyc^1 is a 4-6 membered heterocyclic ring having 1-2 ring nitrogen atoms, wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from the group consisting of C1-C3 alkyl, fluoroC1-C3 alkyl, difluoroC1-C3 alkyl, trifluoroC1-C3 alkyl and OH, or said heterocyclic ring is substituted with a C3-C6 cycloalkylidene ring, or said heterocyclic ring is substituted with an oxo group;

E is

(w) $\text{Ar}^2\text{C}(=\text{O})-$,

(x) $\text{Ar}^2\text{C1-C6 alkyl}-$,

(z) $\text{Ar}^2(\text{C1-C3 alkyl})\text{C}(=\text{O})-$ wherein said alkyl portion is optionally substituted with one or two groups independently selected from the group consisting of OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, C1-C6 alkoxy and $R^e R^f \text{N}-$, where R^e and R^f are independently H or C1-C6 alkyl, or R^e and R^f together with the nitrogen to which they are attached form a 5-6 membered azacyclic ring optionally having an additional ring heteroatom selected from N and O,

(cc) $\text{hetAr}^2(\text{C1-C3 alkyl})\text{C}(=\text{O})-$, wherein said alkyl portion is optionally substituted with one or two groups independently selected from the group consisting of OH, C1-C6 alkyl, hydroxyC1-C6 alkyl, C1-C6 alkoxy and $R^e R^f \text{N}-$, wherein R^e and R^f are independently H or C1-C6 alkyl or R^e and R^f together with the nitrogen to which they are attached form a 5-6 membered azacyclic ring optionally having an additional ring heteroatom selected from N and O,

(dd) $R^1R^2NC(=O)-$,

(oo) $\text{hetAr}^2\text{C1-C6 alkyl-}$,

Ar^2 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl, C1-C6 alkoxy (optionally substituted with 1-3 fluoros), fluoroC1-C6 alkyl, difluoroC1-C6 alkyl, trifluoroC1-C6 alkyl, CN, a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, and R^iR^jN- wherein R^i and R^j are independently H or C1-C6 alkyl;

hetAr^2 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl, C1-C6 alkoxy (optionally substituted with 1-3 fluoros), fluoroC1-C6 alkyl, difluoroC1-C6 alkyl, trifluoroC1-C6 alkyl, hydroxyC1-C6 alkyl, (C3-C6)cycloalkyl, (C1-C6 alkoxy)C1-C6 alkyl, CN, OH, and $R'R''N-$, wherein R' and R'' are independently H or C1-C3 alkyl;

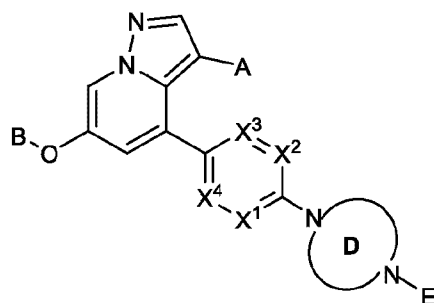
R^1 is H, C1-C6 alkyl or (C1-C6 alkoxy)C1-C6 alkyl; and

R^2 is H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C(=O), hydroxyC1-C6 alkoxy or (3-6C cycloalkyl)CH₂O.

[00358] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is selected from the group consisting of: (S)-4-(6-(4-(2-hydroxy-3-phenylpropanoyl)piperazin-1-yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(1-methyl-1H-pyrazol-4-yl)-4-(6-(4-(2-(pyridin-2-yl)acetyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 4-(6-(4-(2,6-difluorobenzoyl)piperazin-1-yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 2,2,2-trifluoroacetate; 4-(5-(3-cyano-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-N,N-diethylpiperazine-1-carboxamide; 1-(5-(3-cyano-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-N-(2-methoxy-3-methylbutyl)piperidine-4-carboxamide; 4-(6-(4-(2-(5-fluoropyridin-2-yl)acetyl)piperazin-1-yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; bis(2,2,2-trifluoroacetate); 4-(6-(4-(2,6-difluorobenzyl)piperazin-1-yl)pyridine-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 4-(6-(4-(2-methoxybenzyl)piperazin-1-

yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(1-methyl-1H-pyrazol-4-yl)-4-(6-(4-(pyridine-2-ylmethyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 4-(6-(4-((6-methoxypyridin-3-yl)methyl)piperazin-1-yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; or a pharmaceutically acceptable salt or solvate thereof.

[00359] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is a compound of the Formula **IV**:



IV

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X^1 , X^2 , X^3 and X^4 are independently CH, CF, CCH_3 or N, wherein zero, one or two of X^1 , X^2 , X^3 and X^4 is N;

A is H, CN, Cl, CH_3 -, CH_3CH_2 -, cyclopropyl, $-CH_2CN$ or $-CH(CN)CH_3$;

B is

- (a) hydrogen,
- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,
- (d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,
- (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,
- (f) (R^1R^2N)C1-C6 alkyl- wherein said alkyl portion is optionally substituted with OH and wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);
- (g) $hetAr^1$ C1-C3 alkyl-, wherein $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring

heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;

(h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally substituted with OH,

(i) (hetCyc^a)C1-C3 alkyl-,

(j) hetCyc^a-,

(k) C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH,

(l) (C1-C4 alkyl)C(=O)O-C1-C6 alkyl-, wherein each of the C1-C4 alkyl and C1-C6 alkyl portions is optionally and independently substituted with 1-3 fluoros, or

(m) (R¹R²N)C(=O)C1-C6 alkyl-, wherein R¹ and R² are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

hetCyc^a- is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl-, and fluoro, or wherein hetCyc^a is substituted with oxo;

Ring D is (i) a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, (ii) a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, (iii) a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, or (iv) a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

E is

(a) hydrogen,

(b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

(c) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

(d) (C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl,

- (e) (hydroxyC2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros,
- (f) (C1-C6 alkoxy)C(=O)-,
- (g) (C3-C6 cycloalkyl)C(=O)-, wherein said cycloalkyl is optionally substituted with one or more substituents independently selected from C1-C6 alkyl, C1-C6 alkoxy, OH, and (C1-C6 alkoxy)C1-C6 alkyl-, or said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O,
- (h) Ar¹C1-C6 alkyl-,
- (i) Ar¹(C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, C1-C6 alkoxy, R^mRⁿN- or R^mRⁿN-CH₂-, wherein each R^m and Rⁿ is independently H or C1-C6 alkyl,
- (j) hetAr²C1-C6 alkyl-, wherein said alkyl portion is optionally substituted with 1-3 fluoros,
- (k) hetAr²(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy,
- (l) hetAr²C(=O)-,
- (m) hetCyc¹C(=O)-,
- (n) hetCyc¹C1-C6 alkyl-,
- (o) R³R⁴NC(=O)-,
- (p) Ar¹N(R³)C(=O)-,
- (q) hetAr²N(R³)C(=O)-,
- (r) (C1-C6 alkyl)SO₂-, wherein the alkyl portion is optionally substituted with 1-3 fluoros,
- (s) Ar¹SO₂-,
- (t) hetAr²SO₂-,
- (u) N-(C1-C6 alkyl)pyridinonyl,
- (v) Ar¹C(=O)-;
- (w) Ar¹O-C(=O)-,
- (x) (C3-C6 cycloalkyl)(C1-C6 alkyl)C(=O)-,
- (y) (C3-C6 cycloalkyl)(C1-C6 alkyl)SO₂-, wherein the alkyl portion is optionally substituted with 1-3 fluoros,
- (z) Ar¹(C1-C6 alkyl)SO₂-,
- (aa) hetCyc¹-O-C(=O)-,

(bb) $\text{hetCyc}^1\text{CH}_2\text{C}(=\text{O})-$,

(cc) hetAr^2 , or

(dd) C3-C6 cycloalkyl;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), $\text{R}^e\text{R}^f\text{N}-$ wherein R^e and R^f are independently H, C1-C6 alkyl, $(\text{R}^p\text{R}^q\text{N})\text{C1-C6 alkoxy}-$ wherein R^p and R^q are independently H or C1-C6 alkyl, and $(\text{hetAr}^a)\text{C1-C6 alkyl}-$ wherein hetAr^a is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms, or Ar^1 is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

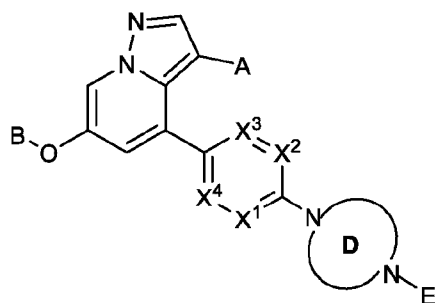
hetAr^2 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein hetAr^2 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), $(\text{C1-C6 alkoxy})\text{C1-C6 alkyl}-$ (optionally substituted with 1-3 fluoros), $\text{R}^e\text{R}^f\text{N}-$ wherein R^e and R^f are independently H or C1-C6 alkyl, OH, $(\text{C1-C6 alkoxy})\text{C1-C6 alkoxy}-$ and C3-C6 cycloalkyl;

hetCyc^1 is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from C1-C6 alkoxy and halogen;

R^3 is H or C1-C6 alkyl; and

R^4 is C1-C6 alkyl.

[00360] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is a compound of the Formula V:



V

or a pharmaceutically acceptable salt and solvate thereof, wherein:

X^1 , X^2 , X^3 and X^4 are independently CH or N, wherein zero, one or two of X^1 , X^2 , X^3 and X^4 is N;

A is CN;

B is

- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,
- (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,
- (f) (R^1R^2N)C1-C6 alkyl-, wherein said alkyl portion is optionally substituted with OH and wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);
- (g) hetAr^1 C1-C3 alkyl-, wherein hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents; or
- (i) (hetCyc^a)C1-C3 alkyl-,

hetCyc^a - is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl- and fluoro, or wherein hetCyc^a is substituted with oxo;

Ring D is (i) a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, or (ii) a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and

optionally having a third ring heteroatom which is oxygen, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

E is

(h) Ar¹C1-C6 alkyl-,

(j) hetAr²C1-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros, or

(l) hetAr²C(=O)-,

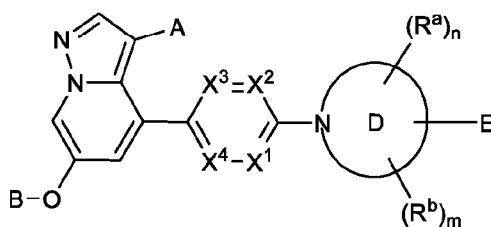
Ar¹ is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, (R^pR^qN)C1-C6 alkoxy- wherein R^p and R^q are independently H or C1-C6 alkyl, and (hetAr^a)C1-C6 alkyl- wherein hetAr^a is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms, or Ar¹ is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O; and

hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein hetAr² is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, OH, (C1-C6 alkoxy)C1-C6 alkoxy- and C3-C6 cycloalkyl.

[00361] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is selected from the group consisting of: 4-(6-(4-benzylpiperazin-1-yl)pyridin-3-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(2-hydroxyethoxy)-4-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; (R)-6-(2-hydroxypropoxy)-4-(6-(4-((6-methoxypyridin-3-yl)methyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(2-methoxyethoxy)-4-(6-(4-((6-

methoxypyridin-3-yl)methyl)piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-(6-methoxynicotinoyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(2-(dimethylamino)ethoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)-6-(2-morpholinoethoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile; 4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)-6-((1-methyl-1H-imidazol-4-yl)methoxy)pyrazolo[1,5-a]pyridine-3-carbonitrile; and 6-ethoxy-4-(5-(6-((5-fluoro-6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrazin-2-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; or a pharmaceutically acceptable salt or solvate thereof.

[00362] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is a compound of Formula **VI**:



VI

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X^1 , X^2 , X^3 and X^4 are independently CH, CCH_3 , CF or N, wherein zero, one or two of X^1 , X^2 , X^3 and X^4 is N;

A is H, CN, Cl, methyl, ethyl or cyclopropyl;

B is:

- (a) hydrogen,
- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,
- (d) dihydroxyC3-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,
- (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

- (f) $(R^1R^2N)C1-C6$ alkyl- where R^1 and R^2 are independently selected from H, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkyl)C(=O)- and (C1-C6 alkoxy)C(=O)-;
- (g) $hetAr^1C1-C3$ alkyl-, where $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;
- (h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally substituted with OH,
- (i) $(hetCyc^a)C1-C3$ alkyl-,
- (j) $hetCyc^a$,
- (k) $(R^1R^2N)C(=O)C1-C6$ alkyl-, where R^1 and R^2 are independently selected from H and C1-C6 alkyl;
- (l) $(R^1R^2N)C(=O)-$, where R^1 and R^2 are independently selected from H and C1-C6 alkyl, or
- (m) $hetCyc^aC(=O)C1-C6$ alkyl-;

$hetCyc^a$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo and (C1-C6 alkoxy)C(=O)-;

Ring D is (i) a saturated monocyclic 4-7 membered heterocyclic ring having one ring heteroatom which is nitrogen, (ii) a saturated 7-8 membered bridged heterocyclic ring having one ring heteroatom which is nitrogen, or (iii) a saturated 7-11 membered heterospirocyclic ring system having one ring heteroatom which is nitrogen;

each R^a is independently C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl or (C1-C6 alkoxy)C1-C6 alkyl-;

R^b is (a) hydroxy, (b) cyclopropyl, (c) $hetCyc^bCH_2-$, (d) $R^iR^jNC(=O)CH_2OCH_2-$ where R^i and R^j are independently H or C1-C6 alkyl, (e) R^cR^dN- , (f) $R^cR^dNCH_2-$, (g) C1-C6 alkoxy-, (h) (C1-C4 alkyl)-C(=O)NH- wherein said alkyl portion is optionally substituted with $hetCyc^b$, $hetAr^a$, C1-C6 alkoxy- or $R'R''N-$, or said alkyl portion is optionally substituted with two substituents independently selected from $R'R''N-$ and OH, where each R' and R'' is independently hydrogen or C1-C6 alkyl, (i) $(R'R''N)C1-C6$ alkoxy $(CH_2)_n-$ where n is 0 or 1 and R' and R'' are independently

hydrogen or C1-C6 alkyl, (j) $\text{hetCyc}^b(\text{C1-C3 alkyl})\text{OCH}_2-$, (k) $\text{hetCyc}^b\text{C}(=\text{O})\text{NH}-$ or (l) $\text{hetAr}^a\text{C}(=\text{O})\text{NH}-$;

hetCyc^b is a 4-6 membered heterocyclic ring, a 7-8 membered bridged heterocyclic ring, or a 7-10 membered heterospirocyclic ring, each ring having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^b is optionally substituted with one or more substituents independently selected from OH, fluoro, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl- (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl-, (C1-C6 alkoxy)C(=O)-, C1-C6 alkoxy, and $\text{R}'\text{R}''\text{N}-$ where R' and R'' are independently hydrogen or C1-C6 alkyl;

hetAr^a is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S wherein hetAr^a is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros),

R^c is hydrogen or C1-C6 alkyl;

R^d is hydrogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C(=O)-, hydroxyC1-C6 alkyl (optionally substituted with 1-3 fluoros), (hydroxyC1-C6 alkyl)C(=O)-, (C1-C6 alkyl)C(=O)-, $(\text{R}^k\text{R}^l\text{N})\text{C1-C6 alkyl}-$ where R^k and R^l are independently H or C1-C6 alkyl, $\text{R}^m\text{R}^n\text{NC}(=\text{O})\text{C1-C6 alkyl}-$ where R^m and R^n are independently H or C1-C6 alkyl, PhCH_2- wherein the phenyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), C3-C6 cycloalkyl, hydroxyC1-C6 alkyl, (C1-C6 alkyl) SO_2- , $\text{R}^e\text{R}^f\text{N}-$ and $(\text{R}^e\text{R}^f\text{N})\text{C1-C6 alkyl}-$ where each R^e and R^f is independently H or C1-C6 alkyl, (C1-C6 alkoxy)C1-C6 alkyl-, or hetCyc^c where hetCyc^c is a 4-6 membered heterocyclic ring having a ring heteroatom selected from N and O and optionally substituted with C1-C6 alkyl;

n is 0, 1, 2, 3, 4, 5 or 6;

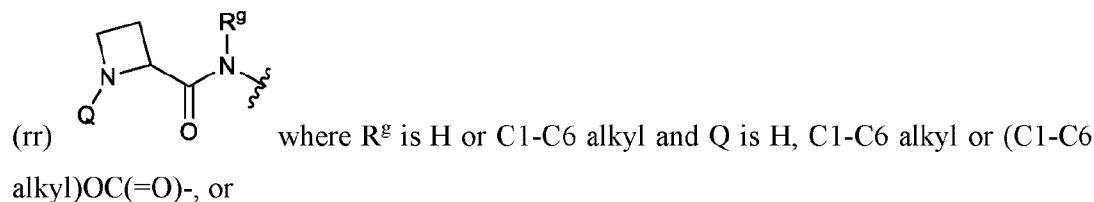
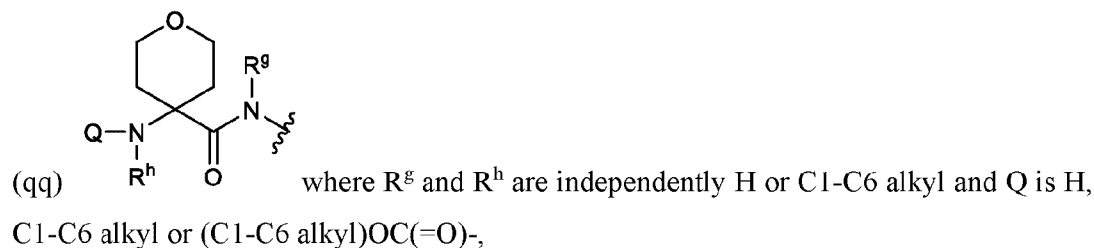
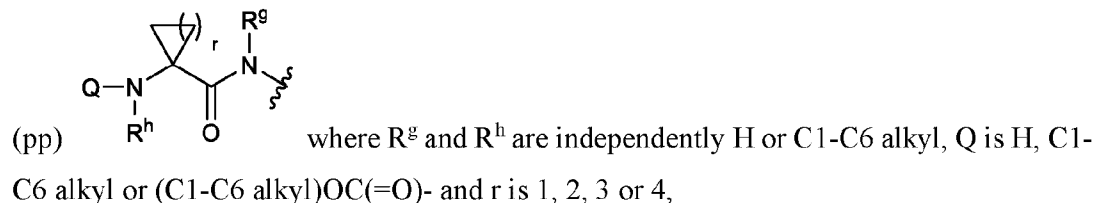
m is 0 or 1;

E is:

- (a) hydrogen,
- (b) hydroxy,
- (c) C1-C6 alkyl optionally substituted with 1-3 fluoros,

- (d) $\text{Ar}^1\text{C1-C6 alkyl-}$ wherein said alkyl portion is optionally substituted with 1-3 fluoros,
- (e) $\text{hetAr}^2\text{C1-C6 alkyl-}$,
- (f) $(\text{C1-C6 alkoxy})\text{C1-C6 alkoxy-}$,
- (g) $\text{Ar}^1\text{O-}$,
- (h) $\text{hetAr}^2\text{-O-}$,
- (i) $\text{Ar}^1\text{NR}^g\text{-}$ where R^g is H or C1-C6 alkyl,
- (j) $\text{hetAr}^2\text{NR}^g\text{-}$ where R^g is H or C1-C6 alkyl,
- (k) $\text{R}^3\text{C(=O)NR}^g\text{-}$ where R^g is H or C1-C6 alkyl;
- (l) $\text{Ar}^1\text{C(=O)NR}^g\text{-}$ where R^g is H or C1-C6 alkyl,
- (m) $\text{hetAr}^2\text{C(=O)NR}^g(\text{CH}_2)_p\text{-}$ where p is 0 or 1 and R^g is H or C1-C6 alkyl,
- (n) $\text{R}^4\text{R}^5\text{NC(=O)-}$,
- (o) $\text{Ar}^1\text{NR}^g\text{C(=O)-}$, where R^g is H or C1-C6 alkyl,
- (p) $\text{hetAr}^2\text{NR}^g\text{C(=O)-}$, where R^g is H or C1-C6 alkyl,
- (q) $\text{Ar}^1(\text{C1-C6 alkyl})\text{C(=O)-}$ wherein said alkyl portion is optionally substituted with OH, hydroxy(C1-C6 alkyl), C1-C6 alkoxy or NH_2 ,
- (r) $\text{hetCyc}^5\text{C(=O)-}$,
- (s) $\text{R}^4\text{R}^5\text{NC(=O)NR}^g\text{-}$ where R^g is H or C1-C6 alkyl, or
- (t) $(\text{C1-C6 alkyl})\text{SO}_2\text{-}$;
- (u) $\text{Ar}^1(\text{C1-C6 alkyl})\text{C(=O)NR}^g\text{-}$ where R^g is H or C1-C6 alkyl,
- (v) $\text{hetAr}^4\text{C(=O)NR}^g\text{-}$ where R^g is H or C1-C6 alkyl,
- (w) $\text{hetAr}^2\text{-S(=O)-}$,
- (x) $(\text{C3-C6 cycloalkyl})\text{CH}_2\text{SO}_2\text{-}$,
- (y) $\text{Ar}^1(\text{C1-C6 alkyl})\text{SO}_2\text{-}$,
- (z) $\text{hetAr}^2\text{SO}_2\text{-}$,
- (aa) Ar^1 ,
- (bb) hetAr^2 ,
- (cc) hetCyc^5 ,
- (dd) C1-C6 alkoxy,
- (ee) $\text{Ar}^1(\text{C1-C6 alkyl})\text{-O-}$,
- (ff) $\text{hetAr}^2(\text{C1-C6 alkyl})\text{-O-}$,
- (gg) $\text{hetAr}^2\text{-O-C1-C6 alkyl-}$,

- (hh) $\text{Ar}^1(\text{C1-C6 alkyl})\text{NR}^g$ - where R^g is H or C1-C6 alkyl,
(ii) $\text{hetAr}^2\text{-S-}$,
(jj) $\text{Ar}^2\text{SO}_2\text{NR}^g(\text{CH}_2)_p$ - where p is 0 or 1 and R^g is H or C1-C6 alkyl,
(kk) $(\text{C1-C6 alkoxy})\text{C(=O)-}$,
(ll) $(\text{C1-C6 alkyl})\text{NR}^g\text{C(=O)O-}$ where R^g is H or C1-C6 alkyl,
(mm) $(\text{C1-C6 alkyl})\text{NR}^g\text{SO}_2$ - where R^g is H or C1-C6 alkyl,
(nn) $\text{hetCyc}^5\text{C(=O)NR}^g$ - where R^g is H or C1-C6 alkyl,
(oo) $\text{Q-NR}^h(\text{C1-C3 alkyl})\text{C(=O)NR}^g$ - where R^g and R^h are independently H or C1-C6 alkyl and Q is H, C1-C6 alkyl or $(\text{C1-C6 alkyl})\text{OC(=O)-}$,



- (ss) $\text{R}^g\text{R}^h\text{N-}$ where R^g and R^h are independently H or C1-C6 alkyl,
(tt) $(\text{C3-C6 cycloalkyl})\text{C(=O)NR}^g$ - where the cycloalkyl is optionally and independently substituted with one or more halogens,
(uu) $(\text{C1-C6 alkyl})\text{C(=O)NR}^g\text{CH}_2$ - where R^g is H or C1-C6 alkyl, or
(vv) $\text{C1-C6 alkylSO}_2\text{NR}^g$ - where R^g is H or C1-C6 alkyl;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), $(\text{C1-C6 alkoxy})\text{C1-C6 alkyl-}$ (optionally substituted with 1-3 fluoros), C3-C6 cycloalkyl, hydroxyC1-C6 alkyl, $(\text{C1-C6 alkyl})\text{SO}_2$ -, $\text{R}^e\text{R}^f\text{N-}$

and (R^eR^fN)C1-C6 alkyl- where each R^e and R^f is independently H or C1-C6 alkyl;

hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S, or a 9-10 membered bicyclic heteroaryl having 1-2 ring nitrogen atoms, wherein hetAr² is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros) and hydroxyC1-C6 alkoxy-;

hetCyc⁵ is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from C1-C6 alkoxy and oxo;

R³ is C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, C3-C6 cycloalkyl, (C3-C6 cycloalkyl)CH₂-, (C3-C6 cycloalkyl)O-, (C3-C6 cycloalkyl)CH₂O-, hetCyc⁷O-, Ph-O-, or (C1-C6 alkoxy)C1-C6 alkyl-; wherein each of said C3-C6 cycloalkyl moieties is optionally substituted with C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy, OH or R'R"N- where R' and R" are independently hydrogen or C1-C6 alkyl;

R⁴ is H or C1-C6 alkyl;

R⁵ is Ar², hetAr³, Ar²CH₂-, hetCyc⁶-CH₂-, hydroxyC1-C6 alkyl-, (C3-C6 cycloalkyl)CH₂-, or C1-C6 alkyl optionally substituted with 1-3 fluoros;

Ar² is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), C3-C6 cycloalkyl, and R^gR^hN- where R^g and R^h are independently H or C1-C6 alkyl, or Ar² is phenyl fused to a 6 membered heterocyclic ring having a ring nitrogen atom and optionally substituted with C1-C6 alkyl;

hetAr³ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), and (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros);

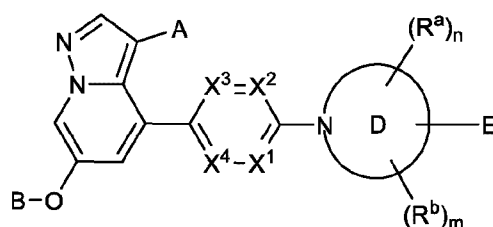
hetAr⁴ is pyridin-4(1H)-onyl or pyridin-2(1H)-onyl optionally substituted with one or more

substituents independently selected from C1-C6 alkyl and halogen;

hetCyc⁶ is a 5-7 membered heterocyclic ring having 1-3 ring heteroatoms independently selected from N, O and S; and

hetCyc⁷ is a 5-7 membered heterocyclic ring having 1-3 ring heteroatoms independently selected from N, O and S.

[00363] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is a compound of the Formula **VII**:



VII

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X¹, X², X³ and X⁴ are independently CH or N, wherein zero, one or two of X¹, X², X³ and X⁴ is N;

A is CN;

B is:

- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, or
- (i) (hetCyc^a)C1-C3 alkyl-;

hetCyc^a is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl, halogen, (C1-C6 alkyl)C(=O)-, C1-C6 alkoxy, oxo, and (C1-C6 alkoxy)C(=O)-;

Ring D is a saturated monocyclic 4-7 membered heterocyclic ring having one ring heteroatom which is nitrogen;

each R^a is independently C1-C6 alkyl (optionally substituted with 1-3 fluoros);

R^b is (a) hydroxy;

n is 0 or 1;

m is 0 or 1;

E is:

(e) $\text{hetAr}^2\text{C1-C6 alkyl-}$,

(h) $\text{hetAr}^2\text{-O-}$,

(k) $\text{R}^3\text{C(=O)NR}^g\text{-}$ where R^g is H or C1-C6 alkyl,

(l) $\text{Ar}^1\text{C(=O)NR}^g\text{-}$ where R^g is H or C1-C6 alkyl, or

(m) $\text{hetAr}^2\text{C(=O)NR}^g(\text{CH}_2)_p\text{-}$ where p is 0 or 1 and R^g is H or C1-C6 alkyl;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), C3-C6 cycloalkyl, hydroxyC1-C6 alkyl, (C1-C6 alkyl) $\text{SO}_2\text{-}$, $\text{R}^e\text{R}^f\text{N-}$ and $(\text{R}^e\text{R}^f\text{N})\text{C1-C6 alkyl-}$ where each R^e and R^f is independently H or C1-C6 alkyl;

hetAr^2 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S, or a 9-10 membered bicyclic heteroaryl having 1-2 ring nitrogen atoms, wherein hetAr^2 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros) and hydroxyC1-C6 alkoxy-; and

R^3 is C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, C3-C6 cycloalkyl, (C3-C6 cycloalkyl) $\text{CH}_2\text{-}$, (C3-C6 cycloalkyl) O- , (C3-C6 cycloalkyl) $\text{CH}_2\text{O-}$, $\text{hetCyc}^7\text{O-}$, Ph-O- , or (C1-C6 alkoxy)C1-C6 alkyl-; wherein each of said C3-C6 cycloalkyl moieties is optionally substituted with C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy, OH, or $\text{R}'\text{R}''\text{N-}$ where R' and R'' are independently hydrogen or C1-C6 alkyl.

[00364] In some embodiments, a RET inhibitor (e.g., a first RET inhibitor or a second RET inhibitor) is selected from the group consisting of: N-(1-(5-(3-cyano-6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)benzamide; 6-ethoxy-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyridin-2-yloxy)azetidin-1-

yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-((6-methoxypyridazin-3-yl)oxy)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; (S)-6-(2-hydroxy-2-methylpropoxy)-4-(6-(3-(pyridin-2-yloxy)pyrrolidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; N-(1-(5-(3-cyano-6-((3-fluoro-1-methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)-5-fluoro-2-methylbenzamide; 3-chloro-N-(1-(5-(3-cyano-6-((3-fluoro-1-methylazetidin-3-yl)methoxy)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-4-methylpiperidin-4-yl)picolinamide; N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)-3-hydroxypiperidin-4-yl)-3-methylbutanamide; 6-(2-hydroxy-2-methylpropoxy)-4-(6-(4-hydroxy-4-(pyridin-2-ylmethyl)piperidin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile; and 3-chloro-N-((3S,4S)-1-(5-(3-cyano-6-ethoxypyrazolo[1,5-a]pyridin-4-yl)pyrazin-2-yl)-3-hydroxypiperidin-4-yl)picolinamide; or a pharmaceutically acceptable salt or solvate thereof.

[00365] Non-limiting examples of receptor tyrosine kinase (e.g., Trk) targeted therapeutic agents, include afatinib, cabozantinib, cetuximab, crizotinib, dabrafenib, entrectinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, pazopanib, panitumumab, pertuzumab, sunitinib, trastuzumab, 1-((3S,4R)-4-(3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea, AG 879, AR-772, AR-786, AR-256, AR-618, AZ-23, AZ623, DS-6051, Gö 6976, GNF-5837, GTx-186, GW 441756, LOXO-101, MGCD516, PLX7486, RXDX101, VM-902A, TPX-0005, and TSR-011. Additional Trk targeted therapeutic agents include those described in U.S. Patent No. 8,450,322; 8,513,263; 8,933,084; 8,791,123; 8,946,226; 8,450,322; 8,299,057; and 8,912,194; U.S. Publication No. 2016/0137654; 2015/0166564; 2015/0051222; 2015/0283132; and 2015/0306086; International Publication No. WO 2010/033941; WO 2010/048314; WO 2016/077841; WO 2011/146336; WO 2011/006074; WO 2010/033941; WO 2012/158413; WO 2014078454; WO 2014078417; WO 2014078408; WO 2014078378; WO 2014078372; WO 2014078331; WO 2014078328; WO 2014078325; WO 2014078323; WO 2014078322; WO 2015175788; WO 2009/013126; WO 2013/174876; WO 2015/124697; WO 2010/058006; WO 2015/017533; WO 2015/112806; WO 2013/183578; and WO 2013/074518.

[00366] Further examples of Trk inhibitors can be found in U.S. Patent No. 8,637,516, International Publication No. WO 2012/034091, U.S. Patent No. 9,102,671, International

Publication No. WO 2012/116217, U.S. Publication No. 2010/0297115, International Publication No. WO 2009/053442, U.S. Patent No. 8,642,035, International Publication No. WO 2009092049, U.S. Patent No. 8,691,221, International Publication No. WO2006131952.

Exemplary Trk inhibitors include GNF-4256, described in *Cancer Chemother. Pharmacol.* 75(1):131-141, 2015; and GNF-5837 (N-[3-[[2,3-dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]-urea), described in *ACS Med. Chem. Lett.* 3(2):140-145, 2012.

[00367] Additional examples of Trk inhibitors include those disclosed in U.S. Publication No. 2010/0152219, U.S. Patent No. 8,114,989, and International Publication No. WO 2006/123113.

Exemplary Trk inhibitors include AZ623, described in *Cancer* 117(6):1321-1391, 2011; AZD6918, described in *Cancer Biol. Ther.* 16(3):477-483, 2015; AZ64, described in *Cancer Chemother. Pharmacol.* 70:477-486, 2012; AZ-23 ((S)-5-Chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine), described in *Mol. Cancer Ther.* 8:1818-1827, 2009; and AZD7451.

[00368] A Trk inhibitor can include those described in U.S. Patent Nos. 7,615,383; 7,384,632; 6,153,189; 6,027,927; 6,025,166; 5,910,574; 5,877,016; and 5,844,092.

[00369] Further examples of Trk inhibitors include CEP-751, described in *Int. J. Cancer* 72:672-679, 1997; CT327, described in *Acta Derm. Venereol.* 95:542-548, 2015; compounds described in International Publication No. WO 2012/034095; compounds described in U.S. Patent No. 8,673,347 and International Publication No. WO 2007/022999; compounds described in U.S. Patent No. 8,338,417; compounds described in International Publication No. WO 2016/027754; compounds described in U.S. Patent No. 9,242,977; compounds described in U.S. Publication No. 2016/0000783; sunitinib (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide), as described in *PLoS One* 9:e95628, 2014; compounds described in International Publication No. WO 2011/133637; compounds described in U.S. Patent No. 8,637,256; compounds described in *Expert. Opin. Ther. Pat.* 24(7):731-744, 2014; compounds described in *Expert Opin. Ther. Pat.* 19(3):305-319, 2009; (R)-2-phenylpyrrolidine substituted imidazopyridazines, e.g., GNF-8625, (R)-1-(6-(6-(2-(3-

fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-[2,4'-bipyridin]-2'-yl)piperidin-4-ol as described in *ACS Med. Chem. Lett.* 6(5):562-567, 2015; GTx-186 and others, as described in *PLoS One* 8(12):e83380, 2013; K252a ((9S-(9 α ,10 β ,12 α))-2,3,9,10,11,12-hexahydro-10-hydroxy-10-(methoxycarbonyl)-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one), as described in *Mol. Cell Biochem.* 339(1-2):201-213, 2010; 4-aminopyrazolylpyrimidines, e.g., AZ-23 (((S)-5-chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine)), as described in *J. Med. Chem.* 51(15):4672-4684, 2008; PHA-739358 (danusertib), as described in *Mol. Cancer Ther.* 6:3158, 2007; Gö 6976 (5,6,7,13-tetrahydro-13-methyl-5-oxo-12H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-12-propanenitrile), as described in *J. Neurochem.* 72:919-924, 1999; GW441756 ((3Z)-3-[(1-methylindol-3-yl)methylidene]-1H-pyrrolo[3,2-b]pyridin-2-one), as described in *IJAE* 115:117, 2010; milciclib (PHA-848125AC), described in *J. Carcinog.* 12:22, 2013; AG-879 ((2E)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-cyano-2-propenethioamide); altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); cabozantinib (N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); lestaurtinib ((5S,6S,8R)-6-Hydroxy-6-(hydroxymethyl)-5-methyl-7,8,14,15-tetrahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[b,h]cycloocta[jkl]cyclopenta[e]-as-indacen-13(6H)-one); dovatatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); ONO-5390556; regorafenib (4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate); and VSR-902A.

[00370] The ability of a Trk inhibitor to act as a TrkA, TrkB, and/or Trk C inhibitor may be tested using the assays described in Examples A and B in U.S. Patent No. 8,513,263,

[00371] In some embodiments, the receptor tyrosine kinase inhibitor is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR). For example, EGFR inhibitors can include osimertinib (merelectinib, Tagrisso), erlotinib (Tarceva), gefitinib (Iressa), cetuximab (Erbix),

necitumumab (Portrazza), neratinib (Nerlynx), lapatinib (Tykerb), panitumumab (Vectibix), and vandetanib (Caprelsa). In some embodiments, the EGFR inhibitor is osimertinib.

[00372] In some embodiments, signal transduction pathway inhibitors include Ras-Raf-MEK-ERK pathway inhibitors (e.g., binimetinib, selumetinib, encorafenib, sorafenib, trametinib, and vemurafenib), PI3K-Akt-mTOR-S6K pathway inhibitors (e.g. everolimus, rapamycin, perifosine, temsirolimus), and other kinase inhibitors, such as baricitinib, brigatinib, capmatinib, danusertib, ibrutinib, milciclib, quercetin, regorafenib, ruxolitinib, semaxanib, AP32788, BLU285, BLU554, INCB39110, INCB40093, INCB50465, INCB52793, INCB54828, MGCD265, NMS-088, NMS-1286937, PF 477736 ((R)-amino-N-[5,6-dihydro-2-(1-methyl-1H-pyrazol-4-yl)-6-oxo-1H-pyrrolo[4,3,2-ef][2,3]benzodiazepin-8-yl]-cyclohexanecetamide), PLX3397, PLX7486, PLX8394, PLX9486, PRN1008, PRN1371, RXDX103, RXDX106, RXDX108, and TG101209 (N-tert-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide).

[00373] Non-limiting examples of checkpoint inhibitors include ipilimumab, tremelimumab, nivolumab, pidilizumab, MPDL3208A, MEDI4736, MSB0010718C, BMS-936559, BMS-956559, BMS-935559 (MDX-1105), AMP-224, and pembrolizumab.

[00374] In some embodiments, cytotoxic chemotherapeutics are selected from arsenic trioxide, bleomycin, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, and vincristine.

[00375] Non-limiting examples of angiogenesis-targeted therapies include aflibercept and bevacizumab.

[00376] The term “immunotherapy” refers to an agent that modulates the immune system. In some embodiments, an immunotherapy can increase the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can decrease the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can recruit and/or enhance the activity of an immune cell.

[00377] In some embodiments, the immunotherapy is a cellular immunotherapy (e.g., adoptive T-cell therapy, dendritic cell therapy, natural killer cell therapy). In some embodiments, the cellular immunotherapy is sipuleucel-T (APC8015; Provenge™; Plosker (2011) *Drugs* 71(1): 101-

108). In some embodiments, the cellular immunotherapy includes cells that express a chimeric antigen receptor (CAR). In some embodiments, the cellular immunotherapy is a CAR-T cell therapy. In some embodiments, the CAR-T cell therapy is tisagenlecleucel (Kymriah™).

[00378] In some embodiments, the immunotherapy is an antibody therapy (e.g., a monoclonal antibody, a conjugated antibody). In some embodiments, the antibody therapy is bevacizumab (Mvasti™, Avastin®), trastuzumab (Herceptin®), avelumab (Bavencio®), rituximab (MabThera™, Rituxan®), edrecolomab (Panorex), daratumumab (Darzalex®), olaratumab (Lartruvo™), ofatumumab (Arzerra®), alemtuzumab (Campath®), cetuximab (Erbix®), oregovomab, pembrolizumab (Keytruda®), dinutuximab (Unituxin®), obinituzumab (Gazyva®), tremelimumab (CP-675,206), ramucirumab (Cyramza®), ublituximab (TG-1101), panitumumab (Vectibix®), elotuzumab (Empliciti™), avelumab (Bavencio®), necitumumab (Portrazza™), cirmutuzumab (UC-961), ibritumomab (Zevalin®), isatuximab (SAR650984), nimotuzumab, fresolimumab (GC1008), lirilumab (INN), mogamulizumab (Poteligeo®), ficlatuzumab (AV-299), denosumab (Xgeva®), ganitumab, urelumab, pidilizumab or amatuximab.

[00379] In some embodiments, the immunotherapy is an antibody-drug conjugate. In some embodiments, the antibody-drug conjugate is gemtuzumab ozogamicin (Mylotarg™), inotuzumab ozogamicin (Besponsa®), brentuximab vedotin (Adcetris®), ado-trastuzumab emtansine (TDM-1; Kadcyla®), mirvetuximab soravtansine (IMGN853) or anetumab ravtansine.

[00380] In some embodiments, the immunotherapy includes blinatumomab (AMG103; Blincyto®) or midostaurin (Rydapt).

[00381] In some embodiments, the immunotherapy includes a toxin. In some embodiments, the immunotherapy is denileukin diftitox (Ontak®).

[00382] In some embodiments, the immunotherapy is a cytokine therapy. In some embodiments, the cytokine therapy is an interleukin 2 (IL-2) therapy, an interferon alpha (IFN α) therapy, a granulocyte colony stimulating factor (G-CSF) therapy, an interleukin 12 (IL-12) therapy, an interleukin 15 (IL-15) therapy, an interleukin 7 (IL-7) therapy or an erythropoietin-alpha (EPO) therapy. In some embodiments, the IL-2 therapy is aldesleukin (Proleukin®). In some embodiments, the IFN α therapy is IntronA® (Roferon-A®). In some embodiments, the G-CSF therapy is filgrastim (Neupogen®).

[00383] In some embodiments, the immunotherapy is an immune checkpoint inhibitor. In some

embodiments, the immunotherapy includes one or more immune checkpoint inhibitors. In some embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the CTLA-4 inhibitor is ipilimumab (Yervoy®) or tremelimumab (CP-675,206). In some embodiments, the PD-1 inhibitor is pembrolizumab (Keytruda®) or nivolumab (Opdivo®). In some embodiments, the PD-L1 inhibitor is atezolizumab (Tecentriq®), avelumab (Bavencio®) or durvalumab (Imfinzi™).

[00384] In some embodiments, the immunotherapy is mRNA-based immunotherapy. In some embodiments, the mRNA-based immunotherapy is CV9104 (see, e.g., Rausch et al. (2014) *Human Vaccin Immunother* 10(11): 3146-52; and Kubler et al. (2015) *J. Immunother Cancer* 3:26).

[00385] In some embodiments, the immunotherapy is bacillus Calmette-Guerin (BCG) therapy.

[00386] In some embodiments, the immunotherapy is an oncolytic virus therapy. In some embodiments, the oncolytic virus therapy is talimogene alherparepvec (T-VEC; Imlygic®).

[00387] In some embodiments, the immunotherapy is a cancer vaccine. In some embodiments, the cancer vaccine is a human papillomavirus (HPV) vaccine. In some embodiments, the HPV vaccine is Gardasil®, Gardasil9® or Cervarix®. In some embodiments, the cancer vaccine is a hepatitis B virus (HBV) vaccine. In some embodiments, the HBV vaccine is Engerix-B®, Recombivax HB® or GI-13020 (Tarmogen®). In some embodiments, the cancer vaccine is Twinrix® or Pediarix®. In some embodiments, the cancer vaccine is BiovaxID®, Oncophage®, GVAX, ADXS11-001, ALVAC-CEA, PROSTVAC®, Rindopepimut®, CimaVax-EGF, lapuleucel-T (APC8024; Neuvenge™), GRNVAC1, GRNVAC2, GRN-1201, hepcortespenlisimut-L (Hepko-V5), DCVAX®, SCIB1, BMT CTN 1401, PrCa VBIR, PANVAC, ProstAtak®, DPX-Survivac, or viagenpumatucel-L (HS-110).

[00388] In some embodiments, the immunotherapy is a peptide vaccine. In some embodiments, the peptide vaccine is neli pepimut-S (E75) (NeuVax™), IMA901, or SurVaxM (SVN53-67). In some embodiments, the cancer vaccine is an immunogenic personal neoantigen vaccine (see, e.g., Ott et al. (2017) *Nature* 547: 217-221; Sahin et al. (2017) *Nature* 547: 222-226). In some embodiments, the cancer vaccine is RGSH4K, or NEO-PV-01. In some embodiments, the cancer vaccine is a DNA-based vaccine. In some embodiments, the DNA-based vaccine is a mammaglobin-A DNA vaccine (see, e.g., Kim et al. (2016) *OncoImmunology* 5(2): e1069940).

[00389] In some embodiments, immune-targeted agents are selected from aldesleukin, interferon alfa-2b, ipilimumab, lambrolizumab, nivolumab, prednisone, and sipuleucel-T.

[00390] Non-limiting examples of radiotherapy include radioiodide therapy, external-beam radiation, and radium 223 therapy.

[00391] Additional kinase inhibitors include those described in, for example, U.S. Patent No. 7,514,446; 7,863,289; 8,026,247; 8,501,756; 8,552,002; 8,815,901; 8,912,204; 9,260,437; 9,273,051; U.S. Publication No. US 2015/0018336; International Publication No. WO 2007/002325; WO 2007/002433; WO 2008/080001; WO 2008/079906; WO 2008/079903; WO 2008/079909; WO 2008/080015; WO 2009/007748; WO 2009/012283; WO 2009/143018; WO 2009/143024; WO WO 2009/014637; 2009/152083; WO 2010/111527; WO 2012/109075; WO 2014/194127; WO 2015/112806; WO 2007/110344; WO 2009/071480; WO 2009/118411; WO 2010/031816; WO 2010/145998; WO 2011/092120; WO 2012/101032; WO 2012/139930; WO 2012/143248; WO 2012/152763; WO 2013/014039; WO 2013/102059; WO 2013/050448; WO 2013/050446; WO 2014/019908; WO 2014/072220; WO 2014/184069; and WO 2016/075224.

[00392] Further examples of kinase inhibitors include those described in, for example, WO 2016/081450; WO 2016/022569; WO 2016/011141; WO 2016/011144; WO 2016/011147; WO 2015/191667; WO 2012/101029; WO 2012/113774; WO 2015/191666; WO 2015/161277; WO 2015/161274; WO 2015/108992; WO 2015/061572; WO 2015/058129; WO 2015/057873; WO 2015/017528; WO/2015/017533; WO 2014/160521; and WO 2014/011900.

[00393] Further examples of kinase inhibitors include luminespib (AUY-922, NVP-AUY922) (5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide) and doramapimod (BIRB-796) (1-[5-tert-butyl-2-(4-methylphenyl)pyrazol-3-yl]-3-[4-(2-morpholin-4-ylethoxy)naphthalen-1-yl]urea).

[00394] Accordingly, also provided herein is a method of treating cancer, comprising administering to a patient in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and the additional therapeutic agent are together effective in treating the cancer.

[00395] In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same.

[00396] These additional therapeutic agents may be administered with one or more doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or pharmaceutical composition thereof, as part of the same or separate dosage forms, via the same or different routes of administration, and/or on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

[00397] Also provided herein is (i) a pharmaceutical combination for treating a cancer in a patient in need thereof, which comprises (a) a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein or known in the art), and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and of the additional therapeutic agent are together effective in treating the cancer; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of cancer; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer in a patient in need thereof. In one embodiment the patient is a human. In some embodiments, the cancer is a RET-associated cancer. For example, a RET-associated cancer having one or more RET inhibitor resistance mutations.

[00398] The term "pharmaceutical combination", as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and at least one additional therapeutic agent (e.g., a chemotherapeutic agent), are both administered to a patient simultaneously in the form of a single composition or dosage. The term "non-fixed combination" means that a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and at least one

additional therapeutic agent (e.g., chemotherapeutic agent) are formulated as separate compositions or dosages such that they may be administered to a patient in need thereof simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients

[00399] Accordingly, also provided herein is a method of treating a cancer, comprising administering to a patient in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and the additional therapeutic agent are together effective in treating the cancer. In one embodiment, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In one embodiment, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g. in daily or intermittently dosages. In one embodiment, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage. In some embodiments, the cancer is a RET-associated cancer. For example, a RET-associated cancer having one or more RET inhibitor resistance mutations. In some embodiments, the additional therapeutic agent is crizotinib. In some embodiments, the additional therapeutic agent is osimertinib. In some embodiments, the patient has been administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, prior to administration of the pharmaceutical composition. In some embodiments, the cancer is a lung cancer (e.g., a RET-associated lung cancer).

[00400] Also provided herein is a method of treating a disease or disorder mediated by RET in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable

salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof. In some embodiments, the disease or disorder mediated by RET is a dysregulation of RET gene, a RET kinase, or expression or activity or level of any of the same. For example the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. A disease or disorder mediated by RET can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of RET, including overexpression and/or abnormal activity levels. In one embodiment, the disease is cancer (e.g., a RET-associated cancer). In one embodiment, the cancer is any of the cancers or RET-associated cancers described herein. In some embodiments, the additional therapeutic agent is crizotinib. In some embodiments, the additional therapeutic agent is osimertinib. In some embodiments, the patient has been administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, prior to administration of the pharmaceutical composition. In some embodiments, the cancer is a lung cancer (e.g., a RET-associated lung cancer).

[00401] Although the genetic basis of tumorigenesis may vary between different cancer types, the cellular and molecular mechanisms required for metastasis appear to be similar for all solid tumor types. During a metastatic cascade, the cancer cells lose growth inhibitory responses, undergo alterations in adhesiveness and produce enzymes that can degrade extracellular matrix components. This leads to detachment of tumor cells from the original tumor, infiltration into the circulation through newly formed vasculature, migration and extravasation of the tumor cells at favorable distant sites where they may form colonies. A number of genes have been identified as being promoters or suppressors of metastasis. For example, overexpression of glial cell-derived neurotrophic factor (GDNF) and its RET receptor tyrosine kinase have been correlated with cancer proliferation and metastasis. See, e.g., Zeng, Q. et al. *J. Int. Med. Res.* (2008) 36(4): 656-64.

[00402] Accordingly, also provided herein are methods for inhibiting, preventing, aiding in the prevention, or decreasing the symptoms of metastasis of a cancer in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or a pharmaceutical composition thereof. Such methods can be used in the treatment of one or more of the cancers described herein. See, e.g., US Publication No. 2013/0029925; International Publication No. WO 2014/083567; and US Patent No. 8,568,998. See also, e.g., Hezam K et al.,

Rev Neurosci 2018 Jan 26;29:93-98; Gao L, et al., *Pancreas* 2015 Jan;44:134-143; Ding K et al., *J Biol Chem* 2014 Jun 6; 289:16057-71; and Amit M et al., *Oncogene* 2017 Jun 8; 36:3232-3239. In some embodiments, the cancer is a RET-associated cancer. In some embodiments, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is used in combination with an additional therapy or another therapeutic agent, including a chemotherapeutic agent, such as a kinase inhibitor. For example, a first or second RET kinase inhibitor. In some embodiments, the additional therapeutic agent is crizotinib. In some embodiments, the additional therapeutic agent is osimertinib. In some embodiments, the patient has been administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, prior to administration of the pharmaceutical composition. In some embodiments, the cancer is a lung cancer (e.g., a RET-associated lung cancer).

[00403] The term “metastasis” is an art known term and means the formation of an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject or patient, where the additional tumor includes the same or similar cancer cells as the primary tumor.

[00404] Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a patient having a RET-associated cancer that include: selecting, identifying, or diagnosing a patient as having a RET-associated cancer, and administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the patient selected, identified, or diagnosed as having a RET-associated cancer. Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a patient having a RET-associated cancer that includes administering a therapeutically effective amount of a Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to a patient having a RET-associated cancer. The decrease in the risk of developing a metastasis or an additional metastasis in a patient having a RET-associated cancer can be compared to the risk of developing a metastasis or an additional metastasis in the patient prior to treatment, or as compared to a patient or a population of patients having a similar or the same RET-associated cancer that has received no treatment or a different treatment. In some embodiments, the RET-associated cancer is a RET-associated cancer having one or more RET inhibitor resistance mutations. In some embodiments, the additional therapeutic agent is crizotinib. In some embodiments, the additional therapeutic agent is

osimertinib. In some embodiments, the patient has been administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, prior to administration of the pharmaceutical composition. In some embodiments, the cancer is a lung cancer (e.g., a RET-associated lung cancer).

[00405] The phrase “risk of developing a metastasis” means the risk that a subject or patient having a primary tumor will develop an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject or patient over a set period of time, where the additional tumor includes the same or similar cancer cells as the primary tumor. Methods for reducing the risk of developing a metastasis in a subject or patient having a cancer are described herein.

[00406] The phrase “risk of developing additional metastases” means the risk that a subject or patient having a primary tumor and one or more additional tumors at sites distant from the primary tumor (where the one or more additional tumors include the same or similar cancer cells as the primary tumor) will develop one or more further tumors distant from the primary tumor, where the further tumors include the same or similar cancer cells as the primary tumor. Methods for reducing the risk of developing additional metastasis are described herein.

[00407] In some embodiments, the presence of one or more RET inhibitor resistance mutations in a tumor causes the tumor to be more resistant to treatment with a first RET inhibitor. Methods useful when a RET inhibitor resistance mutation causes the tumor to be more resistant to treatment with a first RET inhibitor are described below. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and administering to the identified subject a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered in combination with the first RET inhibitor. Also provided are methods of treating a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations that include administering to the subject a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered in combination with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some

embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D.

[00408] For example, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00409] In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668. In some embodiments, the methods further comprise (after (b)) (c) determining whether a

cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00410] In some embodiments, a compound of Formula I-IV is a polymorph form. In some embodiments, the compound is polymorph Form A of the compound of Formula I. In some embodiments, the compound is polymorph Form 1 of the compound of Formula II. In some embodiments, the compound is polymorph Form 2 of the compound of Formula II. In some embodiments, the compound is polymorph Form 7 of the compound of Formula II. In some embodiments, the compound is polymorph Form 8 of the compound of Formula II. In some embodiments, the compound is polymorph Form A of the compound of Formula III. In some embodiments, the compound is polymorph Form A of the compound of Formula IV. In some embodiments, the compound is polymorph Form B of the compound of Formula IV.

[00411] In some embodiments, the compound of Formula I-IV is a pharmaceutically acceptable salt. In some embodiments, the compound is a chloride salt of the compound of Formula I. In some embodiments, the compound is a bromide salt of the compound of Formula I. In some embodiments, the compound is an L-malate salt of the compound of Formula I. In some embodiments, the compound is a D-malate salt of the compound of Formula I. In some embodiments, the compound is a phosphate salt of the compound of Formula II. In some embodiments, the phosphate salt is a sesqui-phosphate salt (*e.g.*, 1.4:1, PO₄:free base).

[00412] In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Tables 2 and 2a in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864,

DS-5010, GSK3179106, GSK3352589, and NMS-E668. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00413] In some embodiments, a compound of Formula I-IV is a polymorph form. In some embodiments, the compound is polymorph Form A of the compound of Formula I. In some embodiments, the compound is polymorph Form 1 of the compound of Formula II. In some embodiments, the compound is polymorph Form 2 of the compound of Formula II. In some embodiments, the compound is polymorph Form 7 of the compound of Formula II. In some embodiments, the compound is polymorph Form 8 of the compound of Formula II. In some embodiments, the compound is polymorph Form A of the compound of Formula III. In some embodiments, the compound is polymorph Form A of the compound of Formula IV. In some embodiments, the compound is polymorph Form B of the compound of Formula IV.

[00414] In some embodiments, the compound of Formula I-IV is a pharmaceutically acceptable salt. In some embodiments, the compound is a chloride salt of the compound of Formula I. In some embodiments, the compound is a bromide salt of the compound of Formula I. In some embodiments, the compound is an L-malate salt of the compound of Formula I. In some embodiments, the compound is a D-malate salt of the compound of Formula I. In some embodiments, the compound is a phosphate salt of the compound of Formula II. In some embodiments, the phosphate salt is a sesqui-phosphate salt (*e.g.*, 1.4:1, PO₄:free base).

[00415] In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-

yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M, G810S, or G810R; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof selected from the group consisting of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00416] In some embodiments, a compound of Formula I-IV is a polymorph form. In some embodiments, the compound is polymorph Form A of the compound of Formula I. In some embodiments, the compound of is polymorph Form 1 of the compound of Formula II. In some embodiments, the compound is polymorph Form 2 of the compound of Formula II. In some embodiments, the compound is polymorph Form 7 of the compound of Formula II. In some embodiments, the compound is polymorph Form 8 of the compound of Formula II. In some embodiments, the compound is polymorph Form A of the compound of Formula III. In some embodiments, the compound is polymorph Form A of the compound of Formula IV. In some embodiments, the compound is polymorph Form B of the compound of Formula IV.

[00417] In some embodiments, the compound of Formula I-IV is a pharmaceutically acceptable salt. In some embodiments, the compound is a chloride salt of the compound of Formula I. In some embodiments, the compound is a bromide salt of the compound of Formula I. In some embodiments, the compound is an L-malate salt of the compound of Formula I. In some embodiments, the compound is a D-malate salt of the compound of Formula I. In some embodiments, the compound is a phosphate salt of the compound of Formula II. In some embodiments, the phosphate salt is a sesqui-phosphate salt (*e.g.*, 1.4:1, PO₄:free base).

[00418] As another example, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In

some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase

protein point mutations/insertions/deletions of Tables 2 and 2a in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M, G810S, or G810R; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00419] As another example, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a second therapeutic agent, wherein the second therapeutic agent is selected from the group consisting of crizotinib and osimertinib, as a monotherapy or in conjunction with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions of Table 2 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering a second therapeutic agent, wherein the second therapeutic agent is selected from the group consisting of crizotinib and osimertinib, as a monotherapy or in conjunction with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments of the above, the RET-associated cancer is a lung cancer.

[00420] In some embodiments, the presence of one or more RET inhibitor resistance mutations in a tumor causes the tumor to be more resistant to treatment with a first RET inhibitor. Methods

useful when a RET inhibitor resistance mutation causes the tumor to be more resistant to treatment with a first RET inhibitor are described below. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and administering to the identified subject a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered in combination with the first RET inhibitor. Also provided are methods of treating a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations that include administering to the subject a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered in combination with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804I, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D.

[00421] In some embodiments provided herein, circulating tumor DNA can be used to monitor the responsiveness of a patient to a particular therapy (e.g., a first RET inhibitor, a second RET inhibitor, or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof). For example, prior to starting treatment with a therapy as described herein (e.g., a first RET inhibitor, a second RET inhibitor, or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof), a biological sample can be obtained from the subject and the level of circulating tumor DNA determined in the biological sample. This sample can be considered a base-line sample. The subject can then be administered one or more doses of a therapy as described herein (e.g., a first RET inhibitor, a second RET inhibitor, or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof) and the levels of circulating tumor DNA can be monitored (e.g., after the first dose, second dose, third dose, etc. or after one week, two weeks, three weeks, four weeks,

etc.). If the level of circulating tumor DNA is lower than the baseline sample (e.g., a 1% to about a 99% reduction, a 1% to about a 95% reduction, a 1% to about a 90% reduction, a 1% to about a 85% reduction, a 1% to about a 80% reduction, a 1% to about a 75% reduction, a 1% reduction to about a 70% reduction, a 1% reduction to about a 65% reduction, a 1% reduction to about a 60% reduction, a 1% reduction to about a 55% reduction, a 1% reduction to about a 50% reduction, a 1% reduction to about a 45% reduction, a 1% reduction to about a 40% reduction, a 1% reduction to about a 35% reduction, a 1% reduction to about a 30% reduction, a 1% reduction to about a 25% reduction, a 1% reduction to about a 20% reduction, a 1% reduction to about a 15% reduction, a 1% reduction to about a 10% reduction, a 1% to about a 5% reduction, about a 5% to about a 99% reduction, about a 10% to about a 99% reduction, about a 15% to about a 99% reduction, about a 20% to about a 99% reduction, about a 25% to about a 99% reduction, about a 30% to about a 99% reduction, about a 35% to about a 99% reduction, about a 40% to about a 99% reduction, about a 45% to about a 99% reduction, about a 50% to about a 99% reduction, about a 55% to about a 99% reduction, about a 60% to about a 99% reduction, about a 65% to about a 99% reduction, about a 70% to about a 99% reduction, about a 75% to about a 95% reduction, about a 80% to about a 99% reduction, about a 90% reduction to about a 99% reduction, about a 95% to about a 99% reduction, about a 5% to about a 10% reduction, about a 5% to about a 25% reduction, about a 10% to about a 30% reduction, about a 20% to about a 40% reduction, about a 25% to about a 50% reduction, about a 35% to about a 55% reduction, about a 40% to about a 60% reduction, about a 50% reduction to about a 75% reduction, about a 60% reduction to about 80% reduction, or about a 65% to about a 85% reduction etc.), this is indicative of responsiveness to the therapy. In some embodiments, the level of circulating tumor DNA is reduced such that it is below the detection limit of the instrument. In some embodiments, the level of circulating tumor DNA in a biological sample obtained from the patient (n) is compared to the sample taken just previous (n-1). If the level of circulating tumor DNA in the n sample is lower than the n-1 sample (e.g., a 1% to about a 99% reduction, a 1% to about a 95% reduction, a 1% to about a 90% reduction, a 1% to about a 85% reduction, a 1% to about a 80% reduction, a 1% to about a 75% reduction, a 1% reduction to about a 70% reduction, a 1% reduction to about a 65% reduction, a 1% reduction to about a 60% reduction, a 1% reduction to about a 55% reduction, a 1% reduction to about a 50% reduction, a 1% reduction to about a 45% reduction, a 1% reduction to about a 40% reduction, a 1% reduction to about a 35% reduction, a 1% reduction to about a 30% reduction,

a 1% reduction to about a 25% reduction, a 1% reduction to about a 20% reduction, a 1% reduction to about a 15% reduction, a 1% reduction to about a 10% reduction, a 1% to about a 5% reduction, about a 5% to about a 99% reduction, about a 10% to about a 99% reduction, about a 15% to about a 99% reduction, about a 20% to about a 99% reduction, about a 25% to about a 99% reduction, about a 30% to about a 99% reduction, about a 35% to about a 99% reduction, about a 40% to about a 99% reduction, about a 45% to about a 99% reduction, about a 50% to about a 99% reduction, about a 55% to about a 99% reduction, about a 60% to about a 99% reduction, about a 65% to about a 99% reduction, about a 70% to about a 99% reduction, about a 75% to about a 95% reduction, about a 80% to about a 99% reduction, about a 90% reduction to about a 99% reduction, about a 95% to about a 99% reduction, about a 5% to about a 10% reduction, about a 5% to about a 25% reduction, about a 10% to about a 30% reduction, about a 20% to about a 40% reduction, about a 25% to about a 50% reduction, about a 35% to about a 55% reduction, about a 40% to about a 60% reduction, about a 50% reduction to about a 75% reduction, about a 60% reduction to about 80% reduction, or about a 65% to about a 85% reduction, etc.), this is indicative of responsiveness to the therapy. In some embodiments, the level of circulating tumor DNA is reduced such that it is below the detection limit of the instrument. In the case of responsiveness to therapy, the subject can to be administered one or more doses of the therapy and the circulating tumor DNA can be continued to be monitored.

[00422] If the level of circulating tumor DNA in the sample is higher than the baseline (e.g., a 1% to about a 99% increase, a 1% to about a 95% increase, a 1% to about a 90% increase, a 1% to about a 85% increase, a 1% to about a 80% increase, a 1% to about a 75% increase, a 1% increase to about a 70% increase, a 1% increase to about a 65% increase, a 1% increase to about a 60% increase, a 1% increase to about a 55% increase, a 1% increase to about a 50% increase, a 1% increase to about a 45% increase, a 1% increase to about a 40% increase, a 1% increase to about a 35% increase, a 1% increase to about a 30% increase, a 1% increase to about a 25% increase, a 1% increase to about a 20% increase, a 1% increase to about a 15% increase, a 1% increase to about a 10% increase, a 1% to about a 5% increase, about a 5% to about a 99% increase, about a 10% to about a 99% increase, about a 15% to about a 99% increase, about a 20% to about a 99% increase, about a 25% to about a 99% increase, about a 30% to about a 99% increase, about a 35% to about a 99% increase, about a 40% to about a 99% increase, about a 45% to about a 99% increase, about a 50% to about a 99% increase, about a 55% to about a 99% increase, about a 60%

to about a 99% increase, about a 65% to about a 99% increase, about a 70% to about a 99% increase, about a 75% to about a 95% increase, about a 80% to about a 99% increase, about a 90% increase to about a 99% increase, about a 95% to about a 99% increase, about a 5% to about a 10% increase, about a 5% to about a 25% increase, about a 10% to about a 30% increase, about a 20% to about a 40% increase, about a 25% to about a 50% increase, about a 35% to about a 55% increase, about a 40% to about a 60% increase, about a 50% increase to about a 75% increase, about a 60% increase to about 80% increase, or about a 65% to about a 85% increase, etc.), this can be indicative of resistance to the therapy. If the level of circulating tumor DNA in the n sample is higher than the n-1 sample (e.g., a 1% to about a 99% increase, a 1% to about a 95% increase, a 1% to about a 90% increase, a 1% to about a 85% increase, a 1% to about a 80% increase, a 1% to about a 75% increase, a 1% increase to about a 70% increase, a 1% increase to about a 65% increase, a 1% increase to about a 60% increase, a 1% increase to about a 55% increase, a 1% increase to about a 50% increase, a 1% increase to about a 45% increase, a 1% increase to about a 40% increase, a 1% increase to about a 35% increase, a 1% increase to about a 30% increase, a 1% increase to about a 25% increase, a 1% increase to about a 20% increase, a 1% increase to about a 15% increase, a 1% increase to about a 10% increase, a 1% to about a 5% increase, about a 5% to about a 99% increase, about a 10% to about a 99% increase, about a 15% to about a 99% increase, about a 20% to about a 99% increase, about a 25% to about a 99% increase, about a 30% to about a 99% increase, about a 35% to about a 99% increase, about a 40% to about a 99% increase, about a 45% to about a 99% increase, about a 50% to about a 99% increase, about a 55% to about a 99% increase, about a 60% to about a 99% increase, about a 65% to about a 99% increase, about a 70% to about a 99% increase, about a 75% to about a 95% increase, about a 80% to about a 99% increase, about a 90% increase to about a 99% increase, about a 95% to about a 99% increase, about a 5% to about a 10% increase, about a 5% to about a 25% increase, about a 10% to about a 30% increase, about a 20% to about a 40% increase, about a 25% to about a 50% increase, about a 35% to about a 55% increase, about a 40% to about a 60% increase, about a 50% increase to about a 75% increase, about a 60% increase to about 80% increase, or about a 65% to about a 85% increase etc.), this can be indicative of resistance to the therapy. When resistance to therapy is suspected, the subject can undergo one or more of imaging, biopsy, surgery, or other diagnostic tests. In some embodiments, when resistance to the therapy is suspected, the subject can be administered (either as a monotherapy or in combination with the previous therapy) a compound

capable of treating a RET inhibitor resistance (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as provided herein). See, for example, Cancer Discov; 7(12); 1368–70 (2017); and Cancer Discov; 7(12); 1394–403 (2017).

[00423] In some embodiments provided herein, a protein biomarker can be used to monitor the responsiveness of a patient to a particular therapy (e.g., a first RET inhibitor, a second RET inhibitor, or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof). For example, prior to starting treatment with a therapy as described herein (e.g., a first RET inhibitor, a second RET inhibitor, or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof), a biological sample can be obtained from the subject and the level of a protein biomarker can be determined in the biological sample. This sample can be considered a base-line sample. The subject can then be administered one or more doses of a therapy as described herein (e.g., a first RET inhibitor, a second RET inhibitor, or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof) and the levels of the protein biomarker can be monitored (e.g., after the first dose, second dose, third dose, etc. or after one week, two weeks, three weeks, four weeks, etc.). If the level of the protein biomarker is lower than the baseline sample (e.g., a 1% to about a 99% reduction, a 1% to about a 95% reduction, a 1% to about a 90% reduction, a 1% to about a 85% reduction, a 1% to about a 80% reduction, a 1% to about a 75% reduction, a 1% reduction to about a 70% reduction, a 1% reduction to about a 65% reduction, a 1% reduction to about a 60% reduction, a 1% reduction to about a 55% reduction, a 1% reduction to about a 50% reduction, a 1% reduction to about a 45% reduction, a 1% reduction to about a 40% reduction, a 1% reduction to about a 35% reduction, a 1% reduction to about a 30% reduction, a 1% reduction to about a 25% reduction, a 1% reduction to about a 20% reduction, a 1% reduction to about a 15% reduction, a 1% reduction to about a 10% reduction, a 1% to about a 5% reduction, about a 5% to about a 99% reduction, about a 10% to about a 99% reduction, about a 15% to about a 99% reduction, about a 20% to about a 99% reduction, about a 25% to about a 99% reduction, about a 30% to about a 99% reduction, about a 35% to about a 99% reduction, about a 40% to about a 99% reduction, about a 45% to about a 99% reduction, about a 50% to about a 99% reduction, about a 55% to about a 99% reduction, about a 60% to about a 99% reduction, about a 65% to about a 99% reduction, about a 70% to about a 99% reduction, about a 75% to about a 95% reduction, about a 80% to about a 99% reduction, about a 90% reduction to about a 99% reduction, about a 95% to

about a 99% reduction, about a 5% to about a 10% reduction, about a 5% to about a 25% reduction, about a 10% to about a 30% reduction, about a 20% to about a 40% reduction, about a 25% to about a 50% reduction, about a 35% to about a 55% reduction, about a 40% to about a 60% reduction, about a 50% reduction to about a 75% reduction, about a 60% reduction to about 80% reduction, or about a 65% to about a 85% reduction etc.), this is indicative of responsiveness to the therapy. In some embodiments, the level of the protein biomarker is reduced such that it is below the detection limit of the instrument. In some embodiments, the level of the protein biomarker in a biological sample obtained from the patient (n) is compared to the sample taken just previous (n-1). If the level of the protein biomarker in the n sample is lower than the n-1 sample (e.g., a 1% to about a 99% reduction, a 1% to about a 95% reduction, a 1% to about a 90% reduction, a 1% to about a 85% reduction, a 1% to about a 80% reduction, a 1% to about a 75% reduction, a 1% reduction to about a 70% reduction, a 1% reduction to about a 65% reduction, a 1% reduction to about a 60% reduction, a 1% reduction to about a 55% reduction, a 1% reduction to about a 50% reduction, a 1% reduction to about a 45% reduction, a 1% reduction to about a 40% reduction, a 1% reduction to about a 35% reduction, a 1% reduction to about a 30% reduction, a 1% reduction to about a 25% reduction, a 1% reduction to about a 20% reduction, a 1% reduction to about a 15% reduction, a 1% reduction to about a 10% reduction, a 1% to about a 5% reduction, about a 5% to about a 99% reduction, about a 10% to about a 99% reduction, about a 15% to about a 99% reduction, about a 20% to about a 99% reduction, about a 25% to about a 99% reduction, about a 30% to about a 99% reduction, about a 35% to about a 99% reduction, about a 40% to about a 99% reduction, about a 45% to about a 99% reduction, about a 50% to about a 99% reduction, about a 55% to about a 99% reduction, about a 60% to about a 99% reduction, about a 65% to about a 99% reduction, about a 70% to about a 99% reduction, about a 75% to about a 95% reduction, about a 80% to about a 99% reduction, about a 90% reduction to about a 99% reduction, about a 95% to about a 99% reduction, about a 5% to about a 10% reduction, about a 5% to about a 25% reduction, about a 10% to about a 30% reduction, about a 20% to about a 40% reduction, about a 25% to about a 50% reduction, about a 35% to about a 55% reduction, about a 40% to about a 60% reduction, about a 50% reduction to about a 75% reduction, about a 60% reduction to about 80% reduction, or about a 65% to about a 85% reduction, etc.), this is indicative of responsiveness to the therapy. In some embodiments, the level of the protein biomarker is reduced such that it is below the detection limit of the instrument. In the case of responsiveness to therapy,

the subject can to be administered one or more doses of the therapy and the protein biomarker can be continued to be monitored.

[00424] If the level of the protein biomarker in the sample is higher than the baseline (e.g., a 1% to about a 99% increase, a 1% to about a 95% increase, a 1% to about a 90% increase, a 1% to about a 85% increase, a 1% to about a 80% increase, a 1% to about a 75% increase, a 1% increase to about a 70% increase, a 1% increase to about a 65% increase, a 1% increase to about a 60% increase, a 1% increase to about a 55% increase, a 1% increase to about a 50% increase, a 1% increase to about a 45% increase, a 1% increase to about a 40% increase, a 1% increase to about a 35% increase, a 1% increase to about a 30% increase, a 1% increase to about a 25% increase, a 1% increase to about a 20% increase, a 1% increase to about a 15% increase, a 1% increase to about a 10% increase, a 1% to about a 5% increase, about a 5% to about a 99% increase, about a 10% to about a 99% increase, about a 15% to about a 99% increase, about a 20% to about a 99% increase, about a 25% to about a 99% increase, about a 30% to about a 99% increase, about a 35% to about a 99% increase, about a 40% to about a 99% increase, about a 45% to about a 99% increase, about a 50% to about a 99% increase, about a 55% to about a 99% increase, about a 60% to about a 99% increase, about a 65% to about a 99% increase, about a 70% to about a 99% increase, about a 75% to about a 95% increase, about a 80% to about a 99% increase, about a 90% increase to about a 99% increase, about a 95% to about a 99% increase, about a 5% to about a 10% increase, about a 5% to about a 25% increase, about a 10% to about a 30% increase, about a 20% to about a 40% increase, about a 25% to about a 50% increase, about a 35% to about a 55% increase, about a 40% to about a 60% increase, about a 50% increase to about a 75% increase, about a 60% increase to about 80% increase, or about a 65% to about a 85% increase, etc.), this can be indicative of resistance to the therapy. If the level of the protein biomarker in the n sample is higher than the n-1 sample (e.g., a 1% to about a 99% increase, a 1% to about a 95% increase, a 1% to about a 90% increase, a 1% to about a 85% increase, a 1% to about a 80% increase, a 1% to about a 75% increase, a 1% increase to about a 70% increase, a 1% increase to about a 65% increase, a 1% increase to about a 60% increase, a 1% increase to about a 55% increase, a 1% increase to about a 50% increase, a 1% increase to about a 45% increase, a 1% increase to about a 40% increase, a 1% increase to about a 35% increase, a 1% increase to about a 30% increase, a 1% increase to about a 25% increase, a 1% increase to about a 20% increase, a 1% increase to about a 15% increase, a 1% increase to about a 10% increase, a 1% to about a 5% increase, about

a 5% to about a 99% increase, about a 10% to about a 99% increase, about a 15% to about a 99% increase, about a 20% to about a 99% increase, about a 25% to about a 99% increase, about a 30% to about a 99% increase, about a 35% to about a 99% increase, about a 40% to about a 99% increase, about a 45% to about a 99% increase, about a 50% to about a 99% increase, about a 55% to about a 99% increase, about a 60% to about a 99% increase, about a 65% to about a 99% increase, about a 70% to about a 99% increase, about a 75% to about a 95% increase, about a 80% to about a 99% increase, about a 90% increase to about a 99% increase, about a 95% to about a 99% increase, about a 5% to about a 10% increase, about a 5% to about a 25% increase, about a 10% to about a 30% increase, about a 20% to about a 40% increase, about a 25% to about a 50% increase, about a 35% to about a 55% increase, about a 40% to about a 60% increase, about a 50% increase to about a 75% increase, about a 60% increase to about 80% increase, or about a 65% to about a 85% increase etc.), this can be indicative of resistance to the therapy. When resistance to therapy is suspected, the subject can undergo one or more of imaging, biopsy, surgery, or other diagnostic tests. In some embodiments, when resistance to the therapy is suspected, the subject can be administered (either as a monotherapy or in combination with the previous therapy) a compound capable of treating a RET inhibitor resistance (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as provided herein).

[00425] In some embodiments, one or more protein biomarkers are monitored. The particular protein biomarkers to be monitored can depend on the type of cancer and can be readily identified by one having ordinary skill in the art. Non-limiting examples of protein biomarkers include: CA 125, carcinoembryonic antigen (CEA), calcitonin, thyroglobulin, adrenocorticotrophic hormone (ACTH), cortisol, CA 19-9, prolactin, hepatocyte growth factor, osteopontin, myeloperoxidase, tissue inhibitor of metalloproteinases 1, angiopoietin-1 (Ang-1), cytokeratin 19 (CK-19), tissue inhibitor of metalloproteinase-1 (TIMP-1), chitinase 3 like-1 (YKL-40), galectin-3 (GAL-3), CYFRA 21-1 (cytokeratins), EPCAM (epithelial cell adhesion molecule), ProGRP (pro-gastrin-releasing peptide), and CEACAM (carcinoembryonic antigen). See, for example, Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*; Published online 18 January 2018. pii: eaar3247. DOI: 10.1126/science.aar3247; Fawaz M Makki et al. Serum biomarkers of papillary thyroid cancer. *J Otolaryngol Head Neck Surg.* 2013; 42(1): 16; and Tatiana N. Zamay et al. Current and Prospective Protein Biomarkers of Lung Cancer. *Cancers* (Basel). 2017 Nov; 9(11): 155. In some

embodiments, the biomarkers include one or more of CEA, calcitonin, thyroglobulin, ACTH, and cortisol. In some embodiments, the cancer is medullary thyroid cancer and the protein biomarkers include CEA and calcitonin. In some embodiments, the cancer is non-medullary thyroid cancer and the protein biomarker include thyroglobulin. In some embodiments, the biomarkers are ACTH and cortisol (e.g., when a patient as Cushing's disease related to their cancer).

[00426] Also provided herein are methods of treating a RET-associated cancer in a subject that include (a) administering one or more (e.g., two or more, three or more, four or more, five or more, or ten or more) doses of a first RET kinase inhibitor to a subject identified or diagnosed as having a RET-associated cancer (e.g., any of the types of RET-associated cancers described herein)(e.g., identified or diagnosed as having a RET-associated cancer using any of the exemplary methods described herein or known in the art); (b) after step (a), determining a level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from the subject; (c) administering a therapeutically effective amount of a second RET inhibitor or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to a subject identified as having about the same or an elevated level of circulating tumor DNA as compared to a reference level of circulating tumor DNA (e.g., any of the reference levels of circulating tumor DNA described herein). In some examples of these methods, the reference level of circulating tumor DNA is a level of circulating tumor DNA in a biological sample obtained from the subject prior to step (a). Some embodiments of these methods further include determining the level of circulating tumor DNA in the biological sample obtained from the subject prior to step (a). In some examples of these methods, the reference level of circulating tumor DNA is a threshold level of circulating tumor DNA (e.g., an average level of circulating tumor DNA in a population of subjects having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment, or a level of circulating tumor DNA in a subject having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment). In some examples of these methods, the first RET inhibitor is selected from the group of: cabozantinib, vandetanib, alectinib, apatinib, sitravatinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864.

[00427] Also provided herein are methods of treating a RET-associated cancer in a subject that include administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, to a subject (i) identified or diagnosed as having a RET-associated cancer (e.g., any of the types of RET-associated cancers described herein) (e.g., identified or diagnosed as having a RET-associated cancer using any of the exemplary methods described herein or known in the art), (ii) previously administered one or more (e.g., two or more, three or more, four or more, five or more, or ten or more) doses of a second RET kinase inhibitor, and (iii) after the prior administration of the one or more doses of the second RET kinase inhibitor, identified as having about the same or an elevated level of circulating tumor DNA as compared to a reference level of circulating tumor DNA (e.g., any of the reference levels of circulating tumor DNA described herein or known in the art). In some embodiments of these methods, the reference level of circulating tumor DNA is a level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, plasma, or serum) obtained from the subject prior to the administration of the one or more doses of the second RET kinase inhibitor. Some embodiments of these methods further include determining the level of circulating tumor DNA in the biological sample obtained from the subject prior to administration of the one or more doses of the second RET kinase inhibitor. In some examples of these methods, the reference level of circulating tumor DNA is a threshold level of circulating tumor DNA (e.g., an average level of circulating tumor DNA in a population of subjects having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment, or a level of circulating tumor DNA in a subject having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment). In some embodiments of these methods, the second RET kinase inhibitor is selected from the group consisting of: cabozantinib, vandetanib, alectinib, apatinib, sitravatinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864.

[00428] Also provided herein are methods of treating a RET-associated cancer in a subject that include: (a) administering one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy to a subject identified or diagnosed as having a RET-associated cancer (e.g., any of the types of RET-

associated cancer described herein) (e.g., a subject identified or diagnosed as having a RET-associated cancer using any of the methods described herein or known in the art); (b) after step (a), determining a level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from the subject; (c) administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and an additional therapeutic agent or treatment (e.g., any of the additional therapeutic agents or treatments of a RET-associated cancer described herein or known in the art) to a subject identified as having about the same or an elevated level of circulating tumor DNA as compared to a reference level of circulating tumor DNA (e.g., any of the exemplary reference levels of circulating tumor DNA described herein or known in the art). In some embodiments of these methods, the additional therapeutic agent is a second RET kinase inhibitor (e.g., a RET kinase inhibitor selected from the group of: cabozantinib, vandetanib, alectinib, apatinib, sitravatinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864. In some examples of any of these methods, the additional therapeutic agent or treatment comprises one or more of: radiation therapy, a chemotherapeutic agent (e.g., any of the exemplary chemotherapeutic agents described herein or known in the art), a checkpoint inhibitor (e.g., any of the exemplary checkpoint inhibitors described herein or known in the art), surgery (e.g., at least partial resection of the tumor) and one or more other kinase inhibitors (e.g., any of the exemplary kinase inhibitors described herein or known in the art). In some examples of these methods, the reference level of circulating tumor DNA is a level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from the subject prior to step (a). In some examples of these methods, the reference level of circulating tumor DNA is a threshold level of circulating tumor DNA (e.g., an average level of circulating tumor DNA in a population of subjects having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment, or a level of circulating tumor DNA in a subject having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment).

[00429] Also provided herein are methods of treating a RET-associated cancer in a subject that include: administering a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and an additional

therapeutic agent or treatment to a subject (i) identified or diagnosed as having a RET-associated cancer (e.g., any of the types of RET-associated cancer described herein) (e.g., a subject identified or diagnosed as having a RET-associated cancer using any of the methods described herein or known in the art), (ii) previously administered one or more doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy, and (ii) after administration of the one or more (e.g., two or more, three or more, four or more, five or more, or ten or more) doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy, identified as having about the same or an elevated level of circulating tumor DNA as compared to a reference level of circulating tumor DNA (e.g., any of the exemplary reference levels of circulating tumor DNA described herein). In some embodiments of these methods, the reference level of circulating tumor DNA is a level of circulating tumor DNA in a biological sample obtained from the subject prior to administration of the one or more (e.g., two or more, three or more, four or more, five or more, or ten or more) doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy. Some embodiments of these methods further include determining the level of circulating tumor DNA in the biological sample obtained from the subject prior to administration of the one or more doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy. In some examples of these methods, the reference level of circulating tumor DNA is a threshold level of circulating tumor DNA (e.g., an average level of circulating tumor DNA in a population of subjects having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment, or a level of circulating tumor DNA in a subject having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment). In some embodiments of this method, the additional therapeutic agent is a second RET kinase inhibitor (e.g., a second RET kinase inhibitor selected from the group of cabozantinib, vandetanib, alectinib, apatinib, sitravatinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864. In some embodiments of these methods, the additional therapeutic agent or treatment includes one or more of radiation therapy, a chemotherapeutic agent (e.g., any of the exemplary chemotherapeutic agents described herein or known in the art), a

checkpoint inhibitor (e.g., any of the exemplary checkpoint inhibitors described herein or known in the art), surgery (e.g., at least partial resection of the tumor), and one or more other kinase inhibitors (e.g., any of the kinase inhibitors described herein or known in the art).

[00430] Also provided herein are methods of selecting a treatment for a subject that include: selecting a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, for a subject (i) identified or diagnosed as having a RET-associated cancer (e.g., any of the RET-associated cancers described herein) (e.g., a subject identified or diagnosed as having a RET-associated cancer using any of the methods described herein or known in the art), (ii) previously administered one or more (e.g., two or more, three or more, four or more, five or more, or ten or more) doses of a second RET kinase inhibitor (e.g., any of the RET kinase inhibitors described herein or known in the art), and (ii) after administration of the one or more doses of the second RET kinase inhibitor, identified as having about the same or an elevated level of circulating tumor DNA as compared to a reference level of circulating tumor DNA. In some embodiments of any of these methods, the reference level of circulating tumor DNA is a level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from the subject prior to administration of the one or more doses of the second RET kinase inhibitor. Some embodiments of these methods further include determining the level of circulating tumor DNA in the biological sample obtained from the subject prior to administration of the one or more doses of the second RET kinase inhibitor. In some examples of these methods, the reference level of circulating tumor DNA is a threshold level of circulating tumor DNA (e.g., an average level of circulating tumor DNA in a population of subjects having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment, or a level of circulating tumor DNA in a subject having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment). In some embodiments of any of these methods, the second RET kinase inhibitor is selected from the group of cabozantinib, vandetanib, alectinib, apatinib, sitravatinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864.

[00431] Also provided herein are methods of selecting a treatment for a subject that include selecting a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically

acceptable salt, amorphous, or polymorph form thereof, and an additional therapeutic agent or treatment for a subject (i) identified or diagnosed as having a RET-associated cancer (e.g., any of the RET-associated cancers described herein or known in the art) (e.g., a subject diagnosed or identified as having a RET-associated cancer using any of the methods described herein or known in the art), (ii) previously administered one or more doses (e.g., two or more, three or more, four or more, five or more, or ten or more) of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy, and (ii) after administration of the one or more doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, identified as having about the same or an elevated level of circulating tumor DNA as compared to a reference level of circulating tumor DNA. In some embodiments of these methods, the reference level of circulating tumor DNA is a level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from the subject prior to administration of the one or more doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy. Some embodiments further include determining the level of circulating tumor DNA in the biological sample obtained from the subject prior to administration of the one or more doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy. In some examples of these methods, the reference level of circulating tumor DNA is a threshold level of circulating tumor DNA (e.g., an average level of circulating tumor DNA in a population of subjects having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment, or a level of circulating tumor DNA in a subject having a similar RET-associated cancer and having a similar stage of the RET-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment). In some embodiments of any of these methods, the additional therapeutic agent is a second RET kinase inhibitor (e.g., a second RET kinase inhibitor selected from the group of: cabozantinib, vandetanib, alectinib, apatinib, sitravatinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864. In some embodiments of any of the methods described herein, the additional therapeutic agent or treatment includes one or more of radiation therapy, a chemotherapeutic agent (e.g., any of the examples of a chemotherapeutic agent described herein or known in the art), a checkpoint inhibitor (e.g., any of the checkpoint inhibitors

described herein or known in the art), surgery (e.g., at least partial resection of the tumor), and one or more other kinase inhibitors (e.g., any of the other kinase inhibitors described herein or known in the art).

[00432] Also provided herein are methods of determining the efficacy of a treatment in a subject that include: (a) determining a first level of circulating tumor DNA in a biological sample (e.g., a biological sample including blood, serum, or plasma) obtained from a subject identified or diagnosed as having a RET-associated cancer at a first time point; (b) administering a treatment including one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject, after the first time point and before a second time point; (c) determining a second level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from the subject at the second time point; and (d) identifying that the treatment is effective in a subject determined to have a decreased second level of circulating tumor DNA as compared to the first level of circulating tumor DNA; or identifying the treatment is not effective in a subject determined to have about the same or an elevated second level of circulating tumor DNA as compared to the first level of circulating tumor DNA. In some embodiments of these methods, the first time point and the second time point are about 1 week to about 1 year apart (e.g., about 1 week to about 10 months, about 1 week to about 8 months, about 1 week to about 6 months, about 1 week to about 4 months, about 1 week to about 3 months, about 1 week to about 2 months, about 1 week to about 1 month, or about 1 week to about 2 weeks).

[00433] Also provided herein are methods of determining whether a subject has developed resistance to a treatment that include: (a) determining a first level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from a subject identified or diagnosed as having a RET-associated cancer at a first time point; (b) administering a treatment including one or more (e.g., two or more, three or more, four or more, five or more, or ten or more) doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject, after the first time point and before a second time point; (c) determining a second level of circulating tumor DNA in a biological sample obtained from the subject at the second time point; and (d) determining that a subject having a decreased second level of circulating tumor DNA as compared to the first level of circulating tumor DNA has not developed resistance to the treatment; or determining that a subject

having about the same or an elevated second level of circulating tumor DNA as compared to the first level of circulating tumor DNA has developed resistance to the treatment. In some embodiments of these methods, the first time point and the second time point are about 1 week to about 1 year apart (e.g., about 1 week to about 10 months, about 1 week to about 8 months, about 1 week to about 6 months, about 1 week to about 4 months, about 1 week to about 3 months, about 1 week to about 2 months, about 1 week to about 1 month, or about 1 week to about 2 weeks).

[00434] Exemplary methods for detecting circulating tumor DNA are described in Moati et al., *Clin. Res. Hepatol. Gastroenterol.* April 4, 2018; Oussalah et al., *EBioMedicine* March 28, 2018; Moon et al., *Adv. Drug Deliv. Rev.* April 4, 2018; Solassaol et al., *Clin. Chem. Lab. Med.* April 7, 2018; Arriola et al., *Clin. Transl. Oncol.* April 5, 2018; Song et al., *J. Circ. Biomark.* March 25, 2018; Aslibekyan et al., *JAMA Cardiol.* April 4, 2018; Isbell et al., *J. Thorac. Cardiovasc. Surg.* March 13, 2018; Boeckx et al., *Clin. Colorectal Cancer* February 22, 2018; Anunobi et al., *J. Surg. Res.* March 28, 2018; Tan et al., *Medicine* 97(13):e0197, 2018; Reithdorf et al., *Transl. Androl. Urol.* 6(6):1090-1110, 2017; Volckmar et al., *Genes Chromosomes Cancer* 57(3):123-139, 2018; and Lu et al., *Chronic Dis. Transl. Med.* 2(4):223-230, 2016. Additional methods for detecting circulating tumor DNA are known in the art.

[00435] In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a multikinase inhibitor, wherein the multikinase inhibitor is selected from vandetanib or cabozantinib; or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the multikinase inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00436] In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation

of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first multikinase inhibitor, wherein the multikinase inhibitor is selected from the group consisting of: vandetanib or cabozantinib; or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the multikinase inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00437] In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Tables 2 and 2a in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a multikinase inhibitor, wherein the multikinase inhibitor is selected from the group consisting of: vandetanib or cabozantinib; or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4, and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the multikinase inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00438] In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a multikinase inhibitor, wherein the multikinase inhibitor is selected from the group consisting of vandetanib or cabozantinib; or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c)

determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M, G810S, or G810R; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof selected from the group consisting of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the multikinase inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00439] As another example, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a multikinase inhibitor (e.g., vandetanib or cabozantinib, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a multikinase inhibitor (e.g., vandetanib or cabozantinib), as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of

step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Tables 2 and 2a in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering a multikinase inhibitor (e.g., vandetanib or cabozantinib), as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M, G810S, or G810R; and (d) administering a multikinase inhibitor (e.g., vandetanib or cabozantinib) as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00440] Also, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some

embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Tables 2 and 2a in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof selected from the group consisting of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in

conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, a second RET inhibitor selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668 is administered in step (d). In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M, G810S, or G810R; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, a second RET inhibitor selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668 is administered in step (d).

[00441] Also, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-

IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) detecting at least one RET inhibitor resistance mutation in a cancer cell in a sample obtained from the subject; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation). In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) detecting at least one RET inhibitor resistance mutation in a cancer cell in a sample obtained from the subject; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation). In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Tables 2 and 2a in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof selected from the group consisting of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) detecting at least one RET inhibitor resistance mutation of Tables 3 or 4 in a cancer cell in a sample obtained from the subject; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET

inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation). In some embodiments, a second RET inhibitor selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668 is administered in step (d). In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprise (after (b)) (c) detecting the RET inhibitor resistance mutation V804M, G810S, or G810R in a cancer cell in a sample obtained from the subject; and (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation). In some embodiments, a second RET inhibitor selected from the group consisting of alectinib, cabozantinib, lenvatinib, nintedanib, ponatinib, regorfenib, sorafenib, sunitinib, vandetanib, RXDX-105 (agerafenib), BLU-667 ((1S,4R)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)cyclohexane-1-carboxamide), BLU6864, DS-5010, GSK3179106, GSK3352589, and NMS-E668 is administered in step (d).

[00442] Further provided herein is a method for treating lung cancer in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, crizotinib, osimertinib, or any combination thereof.

[00443] In some embodiments, the lung cancer is a RET-associated cancer. For example, the method can include: (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the

subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the methods further comprises (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation (e.g., a MET dysregulation such as a MET gene amplification); and (d) administering a second therapeutic agent, wherein the second therapeutic agent is crizotinib, as a monotherapy or in conjunction with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some such embodiments, the method comprises (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions of Table 2 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In further embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation (e.g., a MET dysregulation such as a MET gene amplification); and (d) administering a second therapeutic agent, wherein the second therapeutic agent is crizotinib, as a monotherapy or in conjunction with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00444] In some embodiments, the lung cancer is an EGFR-associated cancer. For example, the method can include: (a) detecting a dysregulation of an EGFR gene, an EGFR kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of an EGFR inhibitor (e.g., osimertinib). In some embodiments, the methods further comprises (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same (e.g., a RET gene

fusion); and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with the EGFR inhibitor (e.g., osimertinib) to the subject if the subject has a cancer cell that has at least one dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same (e.g., a RET gene fusion); or (e) administering additional doses of the EGFR inhibitor (e.g., osimertinib) of step (b) to the subject if the subject has a cancer cell that does not have a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same (e.g., a RET gene fusion). In some such embodiments, the method comprises (a) detecting a dysregulation of an EGFR gene, an EGFR kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of osimertinib. In further embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions of Table 2; and (d) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, as a monotherapy or in conjunction with osimertinib to the subject if the subject has a cancer cell that has one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions of Table 2; or (e) administering additional doses of the osimertinib of step (b) to the subject if the subject has a cancer cell that does not have one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions of Table 2.

[00445] The term “EGFR-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a EGFR gene, a EGFR kinase, or expression or activity, or level of any of the same.

[00446] The phrase “dysregulation of a EGFR gene, a EGFR kinase, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a EGFR gene translocation that results in the expression of a fusion protein, a deletion in a EGFR gene that results in the expression of a EGFR protein that includes a deletion of at least one amino acid as compared to the wild-type EGFR protein, or a mutation in a EGFR gene that results in the expression of a EGFR protein with one or more point mutations, or an alternative spliced version of a EGFR mRNA that results in a EGFR protein that results in the deletion of at least one amino acid in the EGFR protein as compared to the wild-type EGFR protein), or a EGFR gene amplification that results in

overexpression of a EGFR protein or an autocrine activity resulting from the overexpression of a EGFR gene a cell, that results in a pathogenic increase in the activity of a kinase domain of a EGFR protein (*e.g.*, a constitutively active kinase domain of a EGFR protein) in a cell. As another example, a dysregulation of a EGFR gene, a EGFR protein, or expression or activity, or level of any of the same, can be a mutation in a EGFR gene that encodes a EGFR protein that is constitutively active or has increased activity as compared to a protein encoded by a EGFR gene that does not include the mutation. For example, a dysregulation of a EGFR gene, a EGFR protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of EGFR that includes a functional kinase domain, and a second portion of a partner protein (*i.e.*, that is not EGFR). In some examples, dysregulation of a EGFR gene, a EGFR protein, or expression or activity, can be a result of a gene translocation of one EGFR gene with another non-EGFR gene. In some embodiments, the EGFR mutation is a T790M mutation. In some embodiments, the EGFR mutation is a C797S mutation.

[00447] The term “wildtype EGFR” or “wild-type EGFR” describes a nucleic acid (*e.g.*, a EGFR gene or a EGFR mRNA) or protein (*e.g.*, a EGFR protein) that is found in a subject that does not have a EGFR-associated cancer (and optionally also does not have an increased risk of developing a EGFR-associated cancer and/or is not suspected of having a EGFR-associated cancer), or is found in a cell or tissue from a subject that does not have a EGFR-associated cancer (and optionally also does not have an increased risk of developing a EGFR-associated cancer and/or is not suspected of having a EGFR-associated cancer).

[00448] Also provided are methods of selecting a treatment for a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting a treatment that includes administration of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a first RET inhibitor. In some embodiments, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered in combination with the first RET inhibitor. Also provided are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that includes administration of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous,

or polymorph form thereof for a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a first RET inhibitor as a monotherapy that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting the identified subject for a treatment that includes a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a first RET inhibitor as a monotherapy that include: selecting a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations for a treatment that includes administration of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. In some embodiments, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D.

[00449] Also provided are methods of determining the likelihood that a subject having a cancer (e.g., a RET-associated cancer) will have a positive response to treatment with a first RET inhibitor as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations has a decreased likelihood of having a positive response (i.e. an increased likelihood of having a negative response) to treatment with a first RET inhibitor as a monotherapy. Also provided are methods of determining the likelihood that a subject having a cancer (e.g., a RET-associated cancer) will have a positive response to treatment with a first RET inhibitor as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that a subject not having a cancer cell that has one or more RET inhibitor resistance mutations has an increased likelihood of having a positive response to treatment with a first RET inhibitor as a monotherapy as compared to a subject having a cancer cell that has one or more RET inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a first RET inhibitor as a monotherapy in a subject having cancer that include: determining whether a cancer cell in a sample obtained from the subject has

one or more RET inhibitor resistance mutations; and determining that treatment with a first RET inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a first RET inhibitor as a monotherapy in a subject having cancer that include: determining that treatment with a first RET inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D.

[00450] Also provided are methods of treating a subject having a cancer that include: (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (c) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (d) administering additional doses of the first RET inhibitor of step (a) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor of step (a), the subject can also be administered another anticancer agent (e.g., a second RET inhibitor or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy). In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (c), another RET inhibitor can be the first RET inhibitor administered in step (a). In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET

inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D.

[00451] Also provided are methods of treating a subject having a cancer that include: (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (c) administering a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (d) administering additional doses of the first RET inhibitor step (a) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor of step (a), the subject can also be administered another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof). In some embodiments, the additional anticancer agent is an immunotherapy.

[00452] Also provided are methods of treating a subject having a cancer (e.g., a RET-associated cancer) that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor, has one or more RET inhibitor resistance mutations; and (b) administering a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) administering additional doses of the first RET inhibitor previously administered to the subject if the subject has cancer cell that does not

have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor previously administered to the subject, the subject can also be administered another anticancer agent (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or immunotherapy). In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (b), another anticancer agent can be the first RET inhibitor administered in step (a).

[00453] Also provided are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations; and (b) administering a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) administering additional doses of the first RET inhibitor previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor previously administered to the subject, the subject can also be administered another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D. In some embodiments, the additional

anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of (b), another anticancer agent can be the first RET inhibitor administered in step (a).

[00454] In some embodiments, a RET-associated cancer as described herein can occur in a subject along with a dysregulation of another gene, another protein, or the expression or activity or level of any of the same.

[00455] For example, a RET-associated cancer that exhibits a RET fusion can occur in a subject along with one or more of: a dysregulation of a MET gene, a MET protein, or the expression or activity or level of any of the same; a dysregulation of a PIK3CA gene, a PIK3CA protein, or the expression or activity or level of any of the same; a dysregulation of a KRAS gene, a KRAS protein, or the expression or activity or level of any of the same; a dysregulation of a EGFR gene, a EGFR protein, or the expression or activity or level of any of the same (e.g., an amplification of a EGFR gene); a dysregulation of a FGFR2 gene, a FGFR2 protein, or the expression or activity or level of any of the same (eg., a fusion of an FGFR2 gene or an FGFR2 protein); a dysregulation of a CDK4 gene, a CDK4 protein, or the expression or activity or level of any of the same (e.g., an amplification of a CDK4 gene); a dysregulation of a mTOR gene, a mTOR protein, or the expression or activity or level of any of the same; a dysregulation of a CDKN2A gene, a CDKN2A protein, or the expression or activity or level of any of the same (e.g., a deletion in a CDKN2A gene or a CDKN2A protein); a dysregulation of a CDKN2B gene, a CDKN2B protein, or the expression or activity or level of any of the same (e.g., a deletion in a CDKN2B gene or a CDKN2B protein); a dysregulation of a NF1 gene, a NF1 protein, or the expression or activity or level of any of the same; a dysregulation of a MYC gene, a MYC protein, or the expression or activity or level of any of the same (e.g., an amplification in a MYC gene); a dysregulation of a MDM2 gene, a MDM2 protein, or the expression or activity or level of any of the same (e.g., an amplification in a MDM2 gene); a dysregulation of a GNAS gene, a GNAS protein, or the expression or activity or level of any of the same; a dysregulation of a BRCA2 gene, a BRCA2 protein, or the expression or activity or level of any of the same.

[00456] In some embodiments, a RET-associated cancer that exhibits a mutation of a RET gene and/or a RET protein can occur in a subject along with one or more of: a dysregulation of a

PIK3CA gene, a PIK3CA protein, or the expression or activity or level of any of the same; a dysregulation of a KRAS gene, a KRAS protein, or the expression or activity or level of any of the same; a dysregulation of a EGFR gene, a EGFR protein, or the expression or activity or level of any of the same; a dysregulation of a FGFR1 gene, a FGFR1 protein, or the expression or activity or level of any of the same (e.g., an amplification of a FGFR1 gene); a dysregulation of a FGFR2 gene, a FGFR2 protein, or the expression or activity or level of any of the same (e.g., an amplification of a FGFR2 gene); a dysregulation of a FGFR3 gene, a FGFR3 protein, or the expression or activity or level of any of the same (e.g., a fusion of a FGFR3 gene or a FGFR3 protein); a dysregulation of a ERBB2 gene, a ERBB2 protein, or the expression or activity or level of any of the same (e.g., an amplification of ERBB2 gene); and a dysregulation of a KIT gene, a KIT protein, or the expression or activity or level of any of the same.

[00457] In some embodiments, a RET-associated cancer that exhibits an amplification of a RET gene can occur in a patient along with one or more additional kinase amplifications. For example, an amplification in a FGFR1 gene; an amplification in a FGFR2 gene; an amplification in a FGFR3 gene; an amplification of a FGFR4 gene; an amplification of a CDK4 gene; and an amplification in a CDK6 gene.

[00458] In some embodiments, wherein a RET-associated cancer as described herein can occur in a subject along with a dysregulation in another kinase, the methods described herein can further comprise administration of an additional therapeutic agent that targets and/or treats the dysregulation in the other kinase. For example, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the method further comprises (c) detecting a dysregulation in another kinase in a sample from the subject; and (d) administering to the subject a therapeutic agent that targets and/or treats the dysregulation in the other kinase. In some embodiments, the administration of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is done concurrently, sequentially, or serially. In some embodiments, the detecting steps (a) and (c) can be done simultaneously or sequentially in any order.

[00459] Additional therapeutic agents that target and/or treat the dysregulation of the other kinase can include any known inhibitor of the other kinase. Examples of such agents are as follows:

[00460] Exemplary PARP inhibitors include: 3-aminobenzamide (INO-1001), 5-aminoisoquinoline, ABT472, ABT767, AG140361, AG14032, ANG2864, ANG3186, AZD2281, AZD2461, BGP-15, BSI101, BSI401, CEP6800, CEP8983, CK102, CEP9722 (prodrug of CEP8983), CPH101 with CPH102, DR2313, E7016 (GPI-21016), E7449, GP16150, IMP4297, IMP04149, INO1002, INO1003, JPI283, JPI289, KU0687, KU58948, niraparib (MK-4827), NT125, olaparib (AZD2281), ONO-1924H, ONO2231, pamiparib (BGB-290), PJ-34, rucaparib (AG014699), SC10914, SOMCL9112, talazoparib (BMN-673), and veliparib (ABT-888).

[00461] Exemplary CDK 4/6 inhibitors include: palbociclib (PD0332991), abemaciclib (LY2835219), ribociclib (LEE011), trilaciclib (G1T28), voruciclib, and G1T38.

[00462] Exemplary ERBB2 (HER2/neu) inhibitors include: afatinib, afatinib, dacomitinib (PF-00299804), DS8201-a, erlontinib, gefitinib, KU004, lapatinib, lapatinib ditosylate, MM-111, mubritinib (TAK-165), neratinib, pyrotinib (HTI-1001), tucatinib (ONT-380, ARRY-380), 7C3, cetuximab, HER2-BsAb, hersintuzumab, margetuximab, MI130004, NeuVax, paitumumab, pertuzumab, SYD985, trastuzumab, and trastuzumab emtansine.

[00463] Exemplary inhibitors of amplified ERBB2 (HER2/neu) include dacomitinib (PF-00299804), lapatinib, neratinib, pertuzumab, trastuzumab, and trastuzumab emtansine.

[00464] Exemplary EGFR inhibitors include: AC0010, afatinib, AP26113, ASP8273, avatinib, avitinib, AZD3759, BMS-690514, brigatinib, canertinib, Cap-701, CHMFL-EGFR-202, CUDC-101, dacomitinib, EAI045, EGF816, erlontinib, erlotinib, gefitinib, GNS-1481, GNS-1486, Gö6976, HS-10296, icotinib, KU004, lapatinib, nazartinib, neratinib, olmutinib (HM61713, BI 1482694), osimertinib, osimertinib (AZD9291), pelitinib, PF-06747775, PKC412, pyrotinib (HTI-1001), rocilentinib, vandetanib, varlitinib, XL647, 7C3, cetuximab, depatuxizumab mafodotin (ABT-414), matuzumab, nimotuzumab, panitumumab, and zalutumumab.

[00465] Exemplary wild-type EGFR inhibitors include: afatinib, BMS-690514, canertinib, CUDC-101, dacomitinib, erlotinib, gefitinib, lapatinib, neratinib, pelitinib, vandetanib, varlitinib, XL647, cetuximab, matuzumab, nimotuzumab, panitumumab, and zalutumumab.

[00466] Exemplary inhibitors of mutated EGFR include: AC0010, afatinib, AP26113, ASP8273, avatinib, avitinib, AZD3759, BMS-690514, brigatinib, canertinib, Cap-701, CHMFL-EGFR-202, CUDC-101, dacomitinib, EAI045, EGF816, GNS-1481, GNS-1486, Gö6976, HS-

10296, icotinib, nazartinib, neratinib, olmutinib (HM61713, BI 1482694), osimertinib (AZD9291), PF-06747775, PKC412, rocilentinib, vandetanib, varlitinib, and cetuximab.

[00467] An exemplary inhibitor of amplified EGFR is depatuxizumab mafodotin (ABT-414).

[00468] Exemplary inhibitors of FGFR include: ASP5878, AZD4547, BGJ398, BLU9931, brivatinib, cediranib, DEBIO 1347, derazantinib (ARQ-087), dovitinib (CHIR258), E7090, ENMD-2076, erdafitinib (JNJ-42756293), FGF 401, FIIN-1, FRIN-1, INCB054828, L16H50, lenvatinib, lucitanib, LY2874455, nintedanib, NP603, orantinib (SU6668), pazopanib, PBI05204, PD173074, ponatinib, PRN1371, regorafenib, rogaratinib (BAY-1163877), S49076, SOMCL-085, SU5402, sunitinib, TAS-120, FP-1039, GAL-F2, GAL-FR21, GAL-FR22, GAL-FR23, GP369, hLD1.vb, LD1, MFGR1877S, MM-161, PRO-001, and R3Mab.

[00469] Exemplary inhibitors of FGFR fusions include: BGJ398, DEBIO 1347, derazantinib (ARQ-087), E7090, erdafitinib (JNJ-42756293), lucitanib, and TAS-120.

[00470] Exemplary inhibitors of FGFR1, FGFR2, and FGFR3 include: AZD4547, BGJ398, DEBIO 1347, E7090, INCB054828, S49076, SOMCL-085, and TAS-120.

[00471] Exemplary inhibitors of FGF4 include: BLU-554, BLU9931, NVP-FGF401, and hLD1.vb.

[00472] Exemplary inhibitors of amplified FGFR1 include: AZD4547, BGJ398, DEBIO 1347, derazantinib (ARQ-087), erdafitinib (JNJ-42756293), INCB054828, and lucitanib.

[00473] Exemplary inhibitors of amplified FGFR2 include: AZD4547, DEBIO 1347, derazantinib (ARQ-087), lucitanib, regorafenib, and TAS-120.

[00474] An exemplary inhibitor of amplified FGFR3 is AZD4547.

[00475] Exemplary MEK inhibitors include: AZD8330 (ARRY-424704), AZD6244 (ARRY-142866), BI-847325, binimetinib, BIX02188, BIX02189, CH4987655, CH5126766, CI-1040, cobimetinib (GDC-0973), EBI-1051, G-573, G8935, GDC-0623, Myricetin, nobiletin, PD0325901, PD184161, PD318088, PD98059, PD334581, pimasertib (AS-703026), refametinib (RDEA119, BAY 869766), selumetinib (AZD6244), SL-327, TAK-733, trametinib, and U0126.

[00476] Exemplary KRAS inhibitors include: 0375-0604, a covalent quinazoline-based switch II pocket (SIIP) compound, ARS-1620, AZD4785, and LP1.

[00477] Exemplary PI3K inhibitors include: 3-methyladenine, A66, alpelisib (BYL719), AMG319, apitolisib (GDC-0980, RG7422), AS-252424, AS-604850, AS-605240, AZD6842, AZD8186, AZD8835, BGT226 (NVP-BGT226), buparlisib (BKM120), CAY10505, CH5132799,

copanlisib (BAY 80-6946), CUDC-907, CZC24832, dactolisib (BEZ235, NVP-BEZ235), DS7423, duvelisib (IPI-145, INK1197), GDC-0032, GDC-0084, GDC-0326, gedatolisib (PF-05212384, PKI-5587), GNE-317, GS-9820, GSK1059615, GSK2292767, GSK2636771, HS-173, IC-87114, Idelalisib (CAL-101, GS-1101), IPI-145, IPI-3063, IPI-549, LY294002, LY3023414, nemiralisib (GSK2269557), omipalisib (GSK2126458, GSK458), PF-04691502, PF-4989216, PI-103, PI-3065, pictilisib (GDC-0941), PIK-293, PIK-294, PIK-75, PIK-90, PIK-93, PIK-III, pilaralisib (XL147), PKI-587, PP-110, PQR309, PQR309, PW-12, PX-866, quercetin, S14161, SAR245409 (XL765), SAR260301, SAR405, serabelisib (INK-1117, MLN-1117, TAK-1117), SF-1126, SF-2523, SN32976, taselisib (GDC-0032), TB101110, TG100-115, TG100-713, TGR-1202, TGX-221, umbralisib (TGR-1202), voxtalisib (XL765, SAR245409), VPS34-IN1, VS-5584 (SB2343), WJD008, wortmannin, and ZSTK474.

[00478] Exemplary KIT inhibitors include: AMG 706, amuvatinib (MP-470), APcK110, axitinib (AG-013736), AZD2932, dasatinib (BMS-354825), dovitinib (TKI-258, CHIR-258), EXEL-0862, imatinib, KI-328, masitinib (AB1010), midostaurin, MLN518, motesanib, N3-(6-aminopyridin-3-yl)-N1-(2-cyclopentylethyl)-4-methylisophthalamide, nilotinib, OSI-930, pazopanib (GW786034), pexidartinib (PLX3397), PKC412, PLX647, PP1, quizartinib (AC220), regorafenib (BAY 73-4506), semaxinib (SU 5416), sitravatinib (MGCD516), sorafenib, STI571, SU11248, SU9529, sunitinib, telatinib, tivozanib (AV-951), tyrphostin AG 1296, VX-322, and WBZ_4.

[00479] Exemplary MDM2 inhibitors include: (-)-parthenolide, ALRN6924, AM-8553, AMG232, CGM-097, DS-3032b, GEM240, HDM201, HLI98, idasanutlin (RG-7338), JapA, MI-219, MI-219, MI-319, MI-77301 (SAR405838), MK4828, MK-8242, MX69, NSC 207895 (XI-006), Nutlin-3, Nutlin-3a, Nutlin-3b, NVP-CFC218, NVP-CGM097, PXn727/822, RG7112, RO2468, RO5353, RO5503781, serdemetan (JNJ-26854165), SP-141, and YH239-EE.

[00480] Exemplary inhibitors of amplified MDM2 include: AM-8553, AMG232, DS-3032b, MI-77301 (SAR405838), NSC 207895 (XI-006), Nutlin-3a, NVP-CFC218, NVP-CGM097, and RG7112.

[00481] Exemplary inhibitors of MET include: (-)-Oleocanthol, ABBV-399, AMG-208, AMG-337, AMG-458, BAY-853474, BMS-754807, BMS-777607, BMS-794833, cabozantinib (XL184, BMS-907351), capmatinib (INCB28060), crizotinib (PF-02341066), DE605, foretinib (GSK1363089, XL880), glesatinib (MGCD265), golvatinib (E7050), INCB028060, JNJ-

38877605, KRC-408, merestinib (LY2801653), MK-2461, MK8033, NPS-1034, NVP-BVU972, PF-04217903, PHA-665752, S49076, savolitinib (AZD6094, HMPL-504), SGX-523, SU11274, TAS-115, tepotinib (EMD 1214063, MSC2156119J), volitinib, CE-355621, and Onartuzumab.

[00482] Exemplary inhibitors of mTOR include: anthracimycin, apitolisib (GDC-0980, RG7422), AZD-8055, BGT226 (NVP-BGT226), CC-223, CZ415, dactolisib (BEZ235, NVP-BEZ235), DS7423, everolimus (RAD001), GDC-0084, GDC-0349, gedatolisib (PF-05212384, PKI-5587), GSK1059615, INK128, KU-0063794, LY3023414, MLN0128, omipalisib (GSK2126458, GSK458), OSI-027, OSU-53, Palomid 529 (P529), PF-04691502, PI-103, PKI-587, PP242, PQR309, ridafarolimus (AP-23573), sapanisertib (INK 128, MLN0128), SAR245409 (XL765), SF-1126, SF2523, sirolimus (rapamycin), SN32976, TAK228, temsirolimus (CCI-779, NSC 683864), Torin 1, Torin 2, torkinib (PP242), umirolimus, vistusertib (AZD2014), voxtalisib (XL765, SAR245409), VS-5584, VS-5584 (SB2343), WAY-600, WYE-125132 (WYE-132), WYE-354, WYE-687, XL388, and zotarolimus (ABT-578).

[00483] Exemplary inhibitors of MYC include: 10058-F4, 10074-G5, and KSI-3716.

[00484] The phrase “dysregulation of a gene, a protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a kinase domain and a fusion partner, a mutation in a gene that results in the expression of a protein that includes a deletion of at least one amino acid as compared to a wildtype protein, a mutation in a gene that results in the expression of a protein with one or more point mutations as compared to a wildtype protein, a mutation in a gene that results in the expression of a protein with at least one inserted amino acid as compared to a wildtype protein, a gene duplication that results in an increased level of protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of protein in a cell), an alternative spliced version of a mRNA that results in a protein having a deletion of at least one amino acid in the protein as compared to the wild-type protein), or increased expression (e.g., increased levels) of a wildtype protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a gene, a protein, or expression or activity, or level of any of the same, can be a mutation in a gene that encodes a protein that is constitutively active or has increased activity as compared to a protein encoded by a gene that does not include the mutation. For example, a dysregulation of a gene, a protein, or expression or activity, or level of

any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not the primary protein). In some examples, dysregulation of a gene, a protein, or expression or activity or level of any of the same can be a result of a gene translocation of one gene with a different gene.

[00485] Treatment of a patient having a cancer with a multi-kinase inhibitor (MKI) or target-specific kinase inhibitor (e.g., a BRAF inhibitor, a EGFR inhibitor, a MEK inhibitor, an ALK inhibitor, a ROS1 inhibitor, a MET inhibitor, an aromatase inhibitor, a RAF inhibitor, or a RAS inhibitor) can result in dysregulation of a RET gene, a RET kinase, or the expression or activity or level of the same in the cancer, and/or resistance to a RET inhibitor. See, e.g., Bhinge et al., *Oncotarget* 8:27155-27165, 2017; Chang et al., *Yonsei Med. J.* 58:9-18, 2017; and Lopez-Delisle et al., doi: 10.1038/s41388-017-0039-5, *Oncogene* 2018.

[00486] Treatment of a patient having a cancer with a RET inhibitor in combination with a multi-kinase inhibitor or a target-specific kinase inhibitor (e.g., a BRAF inhibitor, a EGFR inhibitor, a MEK inhibitor, an ALK inhibitor, a ROS1 inhibitor, a MET inhibitor, an aromatase inhibitor, a RAF inhibitor, or a RAS inhibitor) can have increased therapeutic efficacy as compared to treatment of the same patient or a similar patient with the RET inhibitor as a monotherapy, or the multi-kinase inhibitor or the target-specific kinase inhibitor as a monotherapy. See, e.g., Tang et al., doi: 10.1038/modpathol.2017.109, *Mod. Pathol.* 2017; Andreucci et al., *Oncotarget* 7:80543-80553, 2017; Nelson-Taylor et al., *Mol. Cancer Ther.* 16:1623-1633, 2017; and Kato et al., *Clin. Cancer Res.* 23:1988-1997, 2017.

[00487] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) and previously administered a multi-kinase inhibitor (MKI) or a target-specific kinase inhibitor (e.g., a BRAF inhibitor, a EGFR inhibitor, a MEK inhibitor, an ALK inhibitor, a ROS1 inhibitor, a MET inhibitor, an aromatase inhibitor, a RAF inhibitor, or a RAS inhibitor) (e.g., as a monotherapy) that include: administering to the patient (i) a therapeutically effective dose of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy, or (ii) a therapeutically effective dose of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and a therapeutically effective dose of the previously administered MKI or the previously administered target-specific kinase inhibitor.

[00488] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) previously administered a MKI or a target specific kinase inhibitor (e.g., a BRAF inhibitor, a EGFR inhibitor, a MEK inhibitor, an ALK inhibitor, a ROS1 inhibitor, a MET inhibitor, an aromatase inhibitor, a RAF inhibitor, or a RAS inhibitor) (e.g., as a monotherapy) that include: identifying a patient having a cancer cell that has a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective dose of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy, or (ii) a therapeutically effective dose of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and a therapeutically effective dose of the previously administered MKI or the previously administered target-specific kinase inhibitor.

[00489] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: administering to a patient a therapeutically effective amount of a MKI or a target-specific kinase inhibitor (e.g., a BRAF inhibitor, a EGFR inhibitor, a MEK inhibitor, an ALK inhibitor, a ROS1 inhibitor, a MET inhibitor, an aromatase inhibitor, a RAF inhibitor, or a RAS inhibitor) (e.g., as a monotherapy) for a first period of time; after the period of time, identifying a patient having a cancer cell that has a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective dose of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy, or (ii) a therapeutically effective dose of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and a therapeutically effective dose of the previously administered MKI or the previously administered target-specific kinase inhibitor.

[00490] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of a BRAF gene, a BRAF kinase, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a BRAF inhibitor (e.g., any of the BRAF inhibitors described herein or known in the art).

[00491] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has

dysregulation of a BRAF gene, a BRAF kinase, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a BRAF inhibitor (e.g., any of the BRAF inhibitors described herein or known in the art).

[00492] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of an EGFR gene, an EGFR protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of an EGFR inhibitor (e.g., any of the EGFR inhibitors described herein or known in the art).

[00493] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of an EGFR gene, an EGFR protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of an EGFR inhibitor (e.g., any of the EGFR inhibitors described herein or known in the art).

[00494] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of a MEK gene, a MEK protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a MEK inhibitor (e.g., any of the MEK inhibitors described herein or known in the art).

[00495] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of a MEK gene, a MEK protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a MEK inhibitor (e.g., any of the MEK inhibitors described herein or known in the art).

[00496] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of an ALK gene, an ALK protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of an ALK inhibitor (e.g., any of the ALK inhibitors described herein or known in the art).

[00497] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of an ALK gene, an ALK protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount an ALK inhibitor (e.g., any of the ALK inhibitors described herein or known in the art).

[00498] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of a ROS gene, a ROS protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a ROS inhibitor (e.g., any of the ROS inhibitors described herein or known in the art).

[00499] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of a ROS gene, a ROS protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount a ROS inhibitor (e.g., any of the ROS inhibitors described herein or known in the art).

[00500] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of a MET gene, a MET protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a MET

inhibitor (e.g., any of the MET inhibitors described herein or known in the art).

[00501] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of a MET gene, a MET protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount a MET inhibitor (e.g., any of the MET inhibitors described herein or known in the art).

[00502] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of an aromatase gene, an aromatase protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of an aromatase inhibitor (e.g., any of the aromatase inhibitors described herein or known in the art).

[00503] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of an aromatase gene, an aromatase protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount an aromatase inhibitor (e.g., any of the aromatase inhibitors described herein or known in the art).

[00504] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of a RAF gene, a RAF protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a RAF inhibitor (e.g., any of the RAF inhibitors described herein or known in the art).

[00505] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of a RAF gene, a RAF protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of

Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount a RAF inhibitor (e.g., any of the RAF inhibitors described herein or known in the art).

[00506] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that has dysregulation of a RAS gene, a RAS protein, or the expression or activity or level of the same that include administering to the patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount of a RAS inhibitor (e.g., any of the RAS inhibitors described herein or known in the art).

[00507] Provided herein are methods of treating a patient having a cancer (e.g., any of the cancers described herein) that include: identifying a patient having a cancer cell that has dysregulation of a RAS gene, a RAS protein, or the expression or activity or level of the same; and administering to the identified patient (i) a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and (ii) a therapeutically effective amount a RAS inhibitor (e.g., any of the RAS inhibitors described herein or known in the art).

[00508] The phrase “dysregulation of a BRAF gene, a BRAF protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a BRAF kinase domain and a fusion partner, a mutation in a BRAF gene that results in the expression of a BRAF protein that includes a deletion of at least one amino acid as compared to a wildtype BRAF protein, a mutation in a BRAF gene that results in the expression of a BRAF protein with one or more point mutations as compared to a wildtype BRAF protein, a mutation in a BRAF gene that results in the expression of a BRAF protein with at least one inserted amino acid as compared to a wildtype BRAF protein, a gene duplication that results in an increased level of BRAF protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of BRAF protein in a cell), an alternative spliced version of a BRAF mRNA that results in a BRAF protein having a deletion of at least one amino acid in the BRAF protein as compared to the wild-type BRAF protein), or increased expression (e.g., increased levels) of a wildtype BRAF protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a

BRAF gene, a BRAF protein, or expression or activity, or level of any of the same, can be a mutation in a BRAF gene that encodes a BRAF protein that is constitutively active or has increased activity as compared to a protein encoded by a BRAF gene that does not include the mutation. For example, a dysregulation of a BRAF gene, a BRAF protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a BRAF protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not BRAF). In some examples, dysregulation of a BRAF gene, a BRAF protein, or expression or activity or level of any of the same can be a result of a gene translocation of one BRAF gene with another non-BRAF gene.

[00509] Non-limiting examples of a BRAF inhibitor include dabrafenib, vemurafenib (also called RG7204 or PLX4032), sorafenib tosylate, PLX-4720, GDC-0879, BMS-908662 (Bristol-Meyers Squibb), LGX818 (Novartis), PLX3603 (Hofmann-LaRoche), RAF265 (Novartis), RO5185426 (Hofmann-LaRoche), and GSK2118436 (GlaxoSmithKline). Additional examples of a BRAF inhibitor are known in the art.

[00510] The phrase “dysregulation of an EGFR gene, an EGFR protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including an EGFR kinase domain and a fusion partner, a mutation in an EGFR gene that results in the expression of an EGFR protein that includes a deletion of at least one amino acid as compared to a wildtype EGFR protein, a mutation in an EGFR gene that results in the expression of an EGFR protein with one or more point mutations as compared to a wildtype EGFR protein, a mutation in an EGFR gene that results in the expression of an EGFR protein with at least one inserted amino acid as compared to a wildtype EGFR protein, a gene duplication that results in an increased level of EGFR protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of EGFR protein in a cell), an alternative spliced version of a EGFR mRNA that results in an EGFR protein having a deletion of at least one amino acid in the EGFR protein as compared to the wild-type EGFR protein), or increased expression (e.g., increased levels) of a wildtype EGFR protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of an EGFR gene, an EGFR protein, or expression or activity, or level of any of the same, can be a

mutation in an EGFR gene that encodes an EGFR protein that is constitutively active or has increased activity as compared to a protein encoded by an EGFR gene that does not include the mutation. For example, a dysregulation of an EGFR gene, an EGFR protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a EGFR protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not EGFR). In some examples, dysregulation of an EGFR gene, an EGFR protein, or expression or activity or level of any of the same can be a result of a gene translocation of one EGFR gene with another non-EGFR gene.

[00511] Non-limiting examples of an EGFR inhibitor include gefitinib, erlotinib, brigatinib, lapatinib, neratinib, icotinib, afatinib, dacomitinib, poziotinib, vandetanib, afatinib, AZD9291, CO-1686, HM61713, AP26113, CI-1033, PKI-166, GW-2016, EKB-569, PDI-168393, AG-1478, CGP-59326A. Additional examples of an EGFR inhibitor are known in the art.

[00512] The phrase “dysregulation of a MEK gene, a MEK protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a MEK kinase domain and a fusion partner, a mutation in a MEK gene that results in the expression of a MEK protein that includes a deletion of at least one amino acid as compared to a wildtype MEK protein, a mutation in a MEK gene that results in the expression of a MEK protein with one or more point mutations as compared to a wildtype MEK protein, a mutation in a MEK gene that results in the expression of a MEK protein with at least one inserted amino acid as compared to a wildtype MEK protein, a gene duplication that results in an increased level of MEK protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of MEK protein in a cell), an alternative spliced version of a MEK mRNA that results in a MEK protein having a deletion of at least one amino acid in the MEK protein as compared to the wild-type MEK protein), or increased expression (e.g., increased levels) of a wildtype MEK protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a MEK gene, a MEK protein, or expression or activity, or level of any of the same, can be a mutation in a MEK gene that encodes a MEK protein that is constitutively active or has increased activity as compared to a protein encoded by a MEK gene that does not include the mutation. For example, a dysregulation

of a MEK gene, a MEK protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a MEK protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not MEK). In some examples, dysregulation of a MEK gene, a MEK protein, or expression or activity or level of any of the same can be a result of a gene translocation of one MEK gene with another non-MEK gene.

[00513] Non-limiting examples of a MEK inhibitor include mekinist, trametinib (GSK1120212), cobimetinib (XL518), binimetinib (MEK162), selumetinib, PD-325901, CI-1040, PD035901, TAK-733, PD098059, U0126, AS703026/MSK1935369, XL-518/GDC-0973, BAY869766/RDEA119, and GSK1120212. Additional examples of a MEK inhibitor are known in the art.

[00514] The phrase “dysregulation of an ALK gene, an ALK protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including an ALK kinase domain and a fusion partner, a mutation in an ALK gene that results in the expression an ALK protein that includes a deletion of at least one amino acid as compared to a wildtype ALK protein, a mutation in an ALK gene that results in the expression of an ALK protein with one or more point mutations as compared to a wildtype ALK protein, a mutation in an ALK gene that results in the expression of an ALK protein with at least one inserted amino acid as compared to a wildtype ALK protein, a gene duplication that results in an increased level of ALK protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of ALK protein in a cell), an alternative spliced version of an ALK mRNA that results in an ALK protein having a deletion of at least one amino acid in the ALK protein as compared to the wild-type ALK protein), or increased expression (e.g., increased levels) of a wildtype ALK protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of an ALK gene, an ALK protein, or expression or activity, or level of any of the same, can be a mutation in an ALK gene that encodes an ALK protein that is constitutively active or has increased activity as compared to a protein encoded by an ALK gene that does not include the mutation. For example, a dysregulation of an ALK gene, an ALK protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of

a fusion protein that contains a first portion of an ALK protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not ALK). In some examples, dysregulation of an ALK gene, an ALK protein, or expression or activity or level of any of the same can be a result of a gene translocation of one ALK gene with another non-ALK gene.

[00515] Non-limiting examples of an ALK inhibitor include crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), dalantercept, ACE-041 (Brigatinib) (AP26113), entrectinib (NMS-E628), PF-06463922 (Pfizer), TSR-011 (Tesaro), CEP-37440 (Teva), CEP-37440 (Teva), X-396 (Xcovery), and ASP-3026 (Astellas). Additional examples of an ALK inhibitor are known in the art.

[00516] The phrase “dysregulation of a ROS1 gene, a ROS1 protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a ROS1 kinase domain and a fusion partner, a mutation in a ROS1 gene that results in the expression a ROS1 protein that includes a deletion of at least one amino acid as compared to a wildtype ROS1 protein, a mutation in a ROS1 gene that results in the expression of a ROS1 protein with one or more point mutations as compared to a wildtype ROS1 protein, a mutation in a ROS1 gene that results in the expression of a ROS1 protein with at least one inserted amino acid as compared to a wildtype ROS1 protein, a gene duplication that results in an increased level of ROS1 protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of ROS1 protein in a cell), an alternative spliced version of a ROS1 mRNA that results in a ROS1 protein having a deletion of at least one amino acid in the ROS1 protein as compared to the wild-type ROS1 protein), or increased expression (e.g., increased levels) of a wildtype ROS1 protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same, can be a mutation in a ROS1 gene that encodes a ROS1 protein that is constitutively active or has increased activity as compared to a protein encoded by a ROS1 gene that does not include the mutation. For example, a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a ROS1 protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not ROS1). In

some examples, dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity or level of any of the same can be a result of a gene translocation of one ROS1 gene with another non-ROS1 gene.

[00517] Non-limiting examples of a ROS1 inhibitor include crizotinib, entrectinib (RXDX-101), lorlatinib (PF-06463922), certinib, TPX-0005, DS-605, and cabozantinib. Additional examples of a ROS1 inhibitor are known in the art.

[00518] The phrase “dysregulation of a MET gene, a MET protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a MET kinase domain and a fusion partner, a mutation in a MET gene that results in the expression a MET protein that includes a deletion of at least one amino acid as compared to a wildtype MET protein, a mutation in a MET gene that results in the expression of a MET protein with one or more point mutations as compared to a wildtype MET protein, a mutation in a MET gene that results in the expression of a MET protein with at least one inserted amino acid as compared to a wildtype MET protein, a gene duplication that results in an increased level of MET protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of MET protein in a cell), an alternative spliced version of a MET mRNA that results in a MET protein having a deletion of at least one amino acid in the MET protein as compared to the wild-type MET protein), or increased expression (e.g., increased levels) of a wildtype MET protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a MET gene, a MET protein, or expression or activity, or level of any of the same, can be a mutation in a MET gene that encodes a MET protein that is constitutively active or has increased activity as compared to a protein encoded by a MET gene that does not include the mutation. For example, a dysregulation of a MET gene, a MET protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a MET protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not MET). In some examples, dysregulation of a MET gene, a MET protein, or expression or activity or level of any of the same can be a result of a gene translocation of one MET gene with another non-MET gene.

[00519] Non-limiting examples of a MET inhibitor include crizotinib, cabozantinib, JNJ-

38877605, PF-04217903 (Pfizer), MK-2461, GSK 1363089, AMG 458 (Amgen), tivantinib, INCB28060 (Incyte), PF-02341066 (Pfizer), E7050 (Eisai), BMS-777607 (Bristol-Meyers Squibb), JNJ-38877605 (Johnson & Johnson), ARQ197 (ArQule), GSK/1363089/XL880 (GSK/Exelixis), and XL174 (BMS/Exelixis). Additional examples of a MET inhibitor are known in the art.

[00520] The phrase “dysregulation of a aromatase gene, an aromatase protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a mutation in an aromatase gene that results in the expression an aromatase protein that includes a deletion of at least one amino acid as compared to a wildtype aromatase protein, a mutation in an aromatase gene that results in the expression of an aromatase protein with one or more point mutations as compared to a wildtype aromatase protein, a mutation in an aromatase gene that results in the expression of an aromatase protein with at least one inserted amino acid as compared to a wildtype aromatase protein, a gene duplication that results in an increased level of aromatase protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of aromatase protein in a cell), an alternative spliced version of an aromatase mRNA that results in an aromatase protein having a deletion of at least one amino acid in the aromatase protein as compared to the wild-type aromatase protein), or increased expression (e.g., increased levels) of a wildtype aromatase in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of an aromatase gene, an aromatase protein, or expression or activity, or level of any of the same, can be a mutation in an aromatase gene that encodes an aromatase protein that is constitutively active or has increased activity as compared to a protein encoded by an aromatase gene that does not include the mutation.

[00521] Non-limiting examples of an aromatase inhibitor include Arimidex (anastrozole), Aromasin (exemestane), Femara (letrozole), Teslac (testolactone), and formestane. Additional examples of an aromatase inhibitor are known in the art.

[00522] The phrase “dysregulation of a RAF gene, a RAF protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a RAF kinase domain and a fusion partner, a mutation in a RAF gene that results in the expression a RAF protein that includes a deletion of at least one amino acid as compared to a wildtype RAF protein, a mutation in a RAF

gene that results in the expression of a RAF protein with one or more point mutations as compared to a wildtype RAF protein, a mutation in a RAF gene that results in the expression of a RAF protein with at least one inserted amino acid as compared to a wildtype RAF protein, a gene duplication that results in an increased level of RAF protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of RAF protein in a cell), an alternative spliced version of a RAF mRNA that results in a RAF protein having a deletion of at least one amino acid in the RAF protein as compared to the wild-type RAF protein), or increased expression (e.g., increased levels) of a wildtype RAF protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a RAF gene, a RAF protein, or expression or activity, or level of any of the same, can be a mutation in a RAF gene that encodes a RAF protein that is constitutively active or has increased activity as compared to a protein encoded by a RAF gene that does not include the mutation. For example, a dysregulation of a RAF gene, a RAF protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a RAF protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not RAF). In some examples, dysregulation of a RAF gene, a RAF protein, or expression or activity or level of any of the same can be a result of a gene translocation of one RAF gene with another non-RAF gene.

[00523] Non-limiting examples of a RAF inhibitor include sorafenib, vemurafenib, dabrafenib, BMS-908662/XL281, GSK2118436, RAF265, RO5126766, and RO4987655. Additional examples of a RAF inhibitor are known in the art.

[00524] The phrase “dysregulation of a RAS gene, a RAS protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a chromosomal translocation that results in the expression of a fusion protein including a RAS kinase domain and a fusion partner, a mutation in a RAS gene that results in the expression a RAS protein that includes a deletion of at least one amino acid as compared to a wildtype RAS protein, a mutation in a RAS gene that results in the expression of a RAS protein with one or more point mutations as compared to a wildtype RAS protein, a mutation in a RAS gene that results in the expression of a RAS protein with at least one inserted amino acid as compared to a wildtype RAS protein, a gene duplication that results in an increased level of RAS protein in a cell, or a mutation in a regulatory sequence

(e.g., a promoter and/or enhancer) that results in an increased level of RAS protein in a cell), an alternative spliced version of a RAS mRNA that results in a RAS protein having a deletion of at least one amino acid in the RAS protein as compared to the wild-type RAS protein), or increased expression (e.g., increased levels) of a wildtype RAS protein in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a RAS gene, a RAS protein, or expression or activity, or level of any of the same, can be a mutation in a RAS gene that encodes a RAS protein that is constitutively active or has increased activity as compared to a protein encoded by a RAS gene that does not include the mutation. For example, a dysregulation of a RAS gene, a RAS protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of a RAS protein that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not RAS). In some examples, dysregulation of a RAS gene, a RAS protein, or expression or activity or level of any of the same can be a result of a gene translocation of one RAS gene with another non-RAS gene.

[00525] Non-limiting examples of a RAS inhibitor include Kobe0065 and Kobe2602. Additional examples of a RAS inhibitor are known in the art.

[00526] Non-limiting examples of multi-kinase inhibitors (MKIs) include dasatinib and sunitinib.

[00527] In some embodiments, provided herein are methods of treating treating a subject having a cancer that include: (a) administering one or more doses of a first RET inhibitor or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one dysregulation of a gene, a protein, or the expression or activity or level of any of the same, wherein the gene or protein is selected from the group consisting of EGFR, MET, ALK, ROS1, KRAS, BRAF, RAS, PIK3CA, and HER2; and (c) administering 1) a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent, 2) administering additional doses of the first RET inhibitor or a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof in combination with an inhibitor targeting the gene or protein (e.g., an inhibitor of EGFR, MET, ALK, ROS1, KRAS, BRAF, RAS, PIK3CA, and HER2), or 3) stop administration of the RET inhibitor of step a) and

administer an inhibitor targeting the gene or protein (e.g., an inhibitor of EGFR, MET, ALK, ROS1, KRAS, BRAF, RAS, PIK3CA, and HER2) to the subject if the subject has a cancer cell that has at least one dysregulation of a gene, a protein, or the expression or activity or level of the same, wherein the gene or protein is selected from the group consisting of EGFR, MET, ALK, ROS1, KRAS, BRAF, RAS, PIK3CA, and HER2; or (d) administering additional doses of the first RET inhibitor step (a) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, the one or more dysregulations of a gene, a protein, or the expression or activity or level of any of the same, wherein the gene or protein is selected from the group consisting of EGFR, MET, ALK, ROS1, KRAS, BRAF, RAS, PIK3CA, and HER2 confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor or the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the tumor is a NSCLC tumor and the one or more dysregulations of a gene, a protein, or the expression or activity or level of any of the same are selected from targetable mutations in EGFR or MET, targetable rearrangements involving ALK or ROS1, or activating mutations in KRAS. In some embodiments, the tumor is a thyroid (non-MTC) tumor and the one or more dysregulations of a gene, a protein, or the expression or activity or level of any of the same are selected from targetable mutations in BRAF or activating mutations in RAS. In some embodiments, the tumor is a MTC tumor and the one or more dysregulations of a gene, a protein, or the expression or activity or level of any of the same are selected from targetable mutations in ALK or activating mutations in RAS. In some embodiments, the tumor is a pancreatic tumor and the one or more dysregulations of a gene, a protein, or the expression or activity or level of any of the same is an activating mutations in KRAS. In some embodiments, the tumor is a colorectal tumor and the one or more dysregulations of a gene, a protein, or the expression or activity or level of any of the same are selected from targetable mutations in BRAF or PIK3CA or an activating mutation in RAS. In some embodiments, the tumor is a breast tumor and the one or more dysregulations of a gene, a protein, or the expression or activity or level of any of the same are selected from targetable mutations in PIK3CA or alteration in HER2.

[00528] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (c) selecting a compound of Formula I-IV, or a

pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more RET inhibitor resistance mutations; or (d) selecting additional doses of the first RET inhibitor of step (a) for the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first RET inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (c), another RET inhibitor can be the first RET inhibitor administered in step (a).

[00529] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (c) selecting a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent if the subject has a cancer cell that has one or more RET inhibitor resistance mutations; or (d) selecting additional doses of the first RET inhibitor of step (a) for the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first RET inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804,

e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the first RET inhibitor administered in step (a).

[00530] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations; (b) selecting a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) selecting additional doses of the first RET inhibitor previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first RET inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof or immunotherapy) for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (c), another RET inhibitor can be the first RET inhibitor administered in step (a).

[00531] Also provided are methods of selecting a treatment for a subject having a cancer that

include (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations; (b) selecting a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) selecting additional doses of the first RET inhibitor previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first RET inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or an immunotherapy) for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the first RET inhibitor administered in step (a).

[00532] Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a first RET inhibitor that include: determining whether a cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and identifying a subject having a cell that has one or more RET inhibitor resistance mutations, as having an increased likelihood of developing a cancer that has some resistance to the first RET inhibitor. Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a first RET inhibitor that include: identifying a subject having a cell that has one or more RET inhibitor resistance mutations, as having an increased likelihood of developing a cancer that has some resistance to the first RET inhibitor. Also provided are methods of determining the presence of a cancer that has some resistance to a first RET inhibitor that include: determining

whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that the subject having a cancer cell that has one or more RET inhibitor resistance mutations has a cancer that has some resistance to the first RET inhibitor. Also provided are methods of determining the presence of a cancer that has some resistance to a first RET inhibitor in a subject that include: determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations, has a cancer that has some resistance to the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D.

[00533] In some embodiments of any of the methods described herein, a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a first RET inhibitor can be any of the RET inhibitor resistance mutations listed in Table 3 or 4 (e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804F, or a substitution at amino acid position 810, e.g., G810S, G810R, G810C, G810A, G810V, and G810D).

[00534] In some embodiments, the presence of one or more RET inhibitor resistance mutations in a tumor causes the tumor to be more resistant to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. Methods useful when a RET inhibitor resistance mutation causes the tumor to be more resistant to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof are described below. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and administering to the identified subject a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy (e.g., a second RET kinase inhibitor). Also provided are methods of treating a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations that include administering to the subject a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or

polymorph form thereof as a monotherapy (e.g., a second RET kinase inhibitor). In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00535] Also provided are methods of selecting a treatment for a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy for the identified subject (e.g., a second RET kinase inhibitor). Also provided are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy (e.g., a second RET kinase inhibitor) for a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy (e.g., a second RET kinase inhibitor) that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting the identified subject for a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy (e.g., a second RET kinase inhibitor). Also provided are methods of selecting a subject having a cancer for a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy (e.g., a second RET kinase inhibitor) that include: selecting a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations for a treatment that does not include a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00536] Also provided are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy that include: determining

whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that the subject having the cancer cell that has one or more RET inhibitor resistance mutations has a decreased likelihood of having a positive response to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy. Also provided are methods of determining the likelihood that a subject having cancer will have a positive response to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy that include: determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations has a decreased likelihood of having a positive response to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy. Also provided are methods of predicting the efficacy of treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy in a subject having cancer that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy in a subject having cancer that include: determining that treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00537] Also provided are methods of treating a subject having a cancer that include: (a) administering one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and (c) administering a second RET inhibitor or a second compound of Formula I-IV,

or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to a subject having a cancer cell that has one or more RET inhibitor resistance mutations; or (d) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (a) to a subject having a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (a), the subject can also be administered another anticancer agent or a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof administered in step (a).

[00538] Also provided are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, has one or more RET inhibitor resistance mutations; (b) administering a second RET inhibitor or a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent to a subject having a cancer cell that has one or more RET inhibitor resistance mutations; or (c) administering additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof previously administered to a subject having a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (a), the subject can also be administered another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a

cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof administered in step (a).

[00539] Also provided are methods of selecting a treatment for a subject having a cancer that include: (a) administering one or more doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and (c) selecting a second RET inhibitor or a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has a RET inhibitor resistance mutation; or (d) selecting additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (a) for the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where additional doses of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (a) are selected for the subject, the method can also include further selecting another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof administered in step (a).

[00540] Also provided are methods of selecting a treatment for a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a compound of Formula I-IV, or a

pharmaceutically acceptable salt, amorphous, or polymorph form thereof, has one or more RET inhibitor resistance mutations; (b) selecting a second RET inhibitor or a second compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has a RET inhibitor resistance mutation; or (c) selecting additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where additional doses of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof of step (a) are selected for the subject, the method can also include further selecting another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof administered in step (a).

[00541] Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof that include: determining whether a cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and identifying the subject if the subject has a cell that has one or more RET inhibitor resistance mutations as having an increased likelihood of developing a cancer that has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof that include: identifying a subject having a cell that has one or more RET inhibitor resistance mutations as having an increased likelihood of developing a cancer that has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. Also provided are methods of determining the presence of a cancer that

has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof that includes: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that the subject having the cancer cell that has one or more RET inhibitor resistance mutations has a cancer that has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. Also provided are methods of determining the presence of a cancer that has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof in a subject that include: determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations has a cancer that has some resistance to a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00542] In some embodiments of any of the methods described herein, a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, can be any of the RET inhibitor resistance mutations listed in Table 3 or 4.

[00543] Methods of determining the level of resistance of a cancer cell or a tumor to a RET inhibitor (e.g., any of the RET inhibitors described herein or known in the art) can be determined using methods known in the art. For example, the level of resistance of a cancer cell to a RET inhibitor can be assessed by determining the IC_{50} of a RET inhibitor (e.g., any of the RET inhibitors described herein or known in the art) on the viability of a cancer cell. In other examples, the level of resistance of a cancer cell to a RET inhibitor can be assessed by determining the growth rate of the cancer cell in the presence of a RET inhibitor (e.g., any of the RET inhibitors described herein). In other examples, the level of resistance of a tumor to a RET inhibitor can be assessed by determining the mass or size of one or more tumors in a subject over time during treatment with a RET inhibitor (e.g., any of the RET inhibitors described herein). In other examples, the level of resistance of a cancer cell or a tumor to a RET inhibitor can be indirectly assessed by determining the activity of a RET kinase including one or more of the RET inhibitor resistance mutations (i.e., the same RET kinase expressed in a cancer cell or a tumor in a subject). The level of resistance of

a cancer cell or tumor having one or more RET inhibitor resistance mutations to a RET inhibitor is relative to the level of resistance in a cancer cell or tumor that does not have a RET inhibitor resistance mutation (e.g., a cancer cell or tumor that does not have the same RET inhibitor resistance mutations, a cancer cell or a tumor that does not have any RET inhibitor resistance mutations, or a cancer cell or a tumor that expresses a wildtype RET protein). For example, the determined level of resistance of a cancer cell or a tumor having one or more RET inhibitor resistance mutations can be greater than about 1%, greater than about 2%, greater than about 3%, greater than about 4%, greater than about 5%, greater than about 6%, greater than about 7%, greater than about 8%, greater than about 9%, greater than about 10%, greater than about 11%, greater than about 12%, greater than about 13%, greater than about 14%, greater than about 15%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, greater than about 150%, greater than about 160%, greater than about 170%, greater than about 180%, greater than about 190%, greater than about 200%, greater than about 210%, greater than about 220%, greater than about 230%, greater than about 240%, greater than about 250%, greater than about 260%, greater than about 270%, greater than about 280%, greater than about 290%, or greater than about 300% of the level of resistance in a cancer cell or tumor that does not have a RET inhibitor resistance mutation (e.g., a cancer cell or tumor that does not have the same RET inhibitor resistance mutations, a cancer cell or a tumor that does not have any RET inhibitor resistance mutations, or a cancer cell or a tumor that expresses a wildtype RET protein).

[00544] RET is thought to play an important role in the development and survival of afferent nociceptors in the skin and gut. RET kinase knock-out mice lack enteric neurons and have other nervous system anomalies suggesting that a functional RET kinase protein product is necessary during development (Taraviras, S. et al., *Development*, 1999, 126:2785-2797). Moreover population studies of patients with Hirschsprung's disease characterized by colonic obstruction due to lack of normal colonic enervation have a higher proportion of both familial and sporadic loss of function RET mutations (Butler Tjaden N., et al., *Transl. Res.*, 2013, 162: 1-15). Irritable bowel syndrome (IBS) is a common illness affecting 10-20% of individuals in developed countries and is characterized by abnormal bowel habits, bloating and visceral hypersensitivity (Camilleri, M.,

N. Engl. J. Med., 2012, 367: 1626-1635). While the etiology of IBS is unknown it is thought to result from either a disorder between the brain and gastrointestinal tract, a disturbance in the gut microbiome or increased inflammation. The resulting gastrointestinal changes affect normal bowel transit resulting in either diarrhea or constipation. Furthermore in many IBS patients the sensitization of the peripheral nervous system results in visceral hypersensitivity or allodynia (Keszthelyi, D., *Eur. J. Pain*, 2012, 16: 1444-1454). See, e.g., U.S. Publication No. 2015/0099762.

[00545] Accordingly, provided herein are methods for treating a patient diagnosed with (or identified as having) an irritable bowel syndrome (IBS) including diarrhea-predominant, constipation- predominant or alternating stool pattern, functional bloating, functional constipation, functional diarrhea, unspecified functional bowel disorder, functional abdominal pain syndrome, chronic idiopathic constipation, functional esophageal disorders, functional gastroduodenal disorders, functional anorectal pain, and inflammatory bowel disease that include administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00546] Also provided herein are methods for treating a patient identified or diagnosed as having a RET-associated irritable bowel syndrome (IBS) (e.g., a patient that has been identified or diagnosed as having a RET-associated irritable bowel syndrome (IBS) through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient) that include administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00547] Also provided herein are methods for treating pain associated with IBS that include administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof is administered in combination with another therapeutic agent useful for treating one or more symptoms of IBS.

[00548] Also provided are methods for treating an irritable bowel syndrome (IBS) in a patient in need thereof, the method comprising: (a) determining if the irritable bowel syndrome (IBS) in the patient is a RET-associated IBS (e.g., using a regulatory-agency approved, e.g., FDA-

approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient, or by performing any of the non-limiting examples of assays described herein); and (b) if the IBS is determined to be a RET-associated IBS, administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof.

[00549] In some embodiments, the compounds of the present invention are useful for treating irritable bowel syndrome (IBS) in combination with one or more additional therapeutic agents or therapies effective in treating the irritable bowel syndrome that work by the same or a different mechanism of action. The at least one additional therapeutic agent may be administered with a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

[00550] Non-limiting examples of additional therapeutics for the treatment of irritable bowel syndrome (IBS) include probiotics, fiber supplements (e.g., psyllium, methylcellulose), anti-diarrheal medications (e.g., loperamide), bile acid binders (e.g., cholestyramine, colestipol, colesevelam), anticholinergic and antispasmodic medications (e.g., hyoscyamine, dicyclomine), antidepressant medications (e.g., tricyclic antidepressant such as imipramine or nortriptyline or a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine or paroxetine), antibiotics (e.g., rifaximin), alosetron, and lubiprostone.

[00551] Accordingly, also provided herein are methods of treating irritable bowel syndrome (IBS), comprising administering to a patient in need thereof a pharmaceutical combination for treating IBS which comprises (a) a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of IBS, wherein the amounts of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and the additional therapeutic agent are together effective in treating the IBS. In one embodiment, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In one embodiment, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form

thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g. in daily or intermittently dosages. In one embodiment, compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage.

[00552] Also provided herein is (i) a pharmaceutical combination for treating irritable bowel syndrome in a patient in need thereof, which comprises (a) a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein for treating irritable bowel syndrome or known in the art), and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of irritable bowel syndrome, wherein the amounts of the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and of the additional therapeutic agent are together effective in treating the irritable bowel syndrome; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of irritable bowel syndrome; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of irritable bowel syndrome in a patient in need thereof. In one embodiment the patient is a human.

[00553] The term "pharmaceutical combination", as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and at least one additional therapeutic agent (e.g., an agent effective in treating irritable bowel syndrome), are both administered to a patient simultaneously in the form of a single composition or dosage. The term "non-fixed combination" means that a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and at least one additional therapeutic agent (e.g., an agent effective in treating irritable bowel syndrome) are formulated as separate compositions or dosages, such that they may be administered to a patient in need thereof simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds

in the body of the patient. In one embodiment, the compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof and the additional therapeutic agent are formulated as separate unit dosage forms, wherein the separate dosage forms are suitable for either sequential or simultaneous administration. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients.

[00554] In some embodiments, a compound provided herein can be used as an agent for supportive care for a patient undergoing cancer treatment. For example, a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, can be useful to reduce one or more symptoms associated with treatment with one or more cancer therapies such as diarrhea or constipations complications and/or abdominal pain. See, for example, U.S. Publication No. 2015/0099762 and Hoffman, J.M. et al. *Gastroenterology* (2012) 142:844-854. Accordingly, a compound, or a pharmaceutically acceptable salt thereof, or composition provided herein can be administered to a patient to address one or more complications associated with cancer treatment (e.g., gastrointestinal complications such as diarrhea, constipation, or abdominal pain).

[00555] In some embodiments, a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, can be administered to a patient undergoing cancer treatment (e.g., a patient experiencing an adverse event associated with cancer treatment such as an immune-related adverse event or a gastrointestinal complication including diarrhea, constipation, and abdominal pain). For example, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be used in the treatment of colitis or IBS associated with administration of a checkpoint inhibitor; see, e.g., Postow, M.A. et al. *Journal of Clinical Oncology* (2015) 33: 1974-1982. In some such embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be formulated to exhibit low bioavailability and/or be targeted for delivery in the gastrointestinal tract. See, for example, US Patent No. 6,531,152.

[00556] Also provided is a method for inhibiting RET kinase activity in a cell, comprising contacting the cell with a compound of Formula I. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo. In one embodiment, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to a subject having a cell having RET kinase activity. In some embodiments, the cell is a cancer cell. In one

embodiment, the cancer cell is any cancer as described herein. In some embodiments, the cancer cell is a RET-associated cancer cell. In some embodiments, the cell is a gastrointestinal cell.

[00557] Also provided is a method for inhibiting RET kinase activity in a mammalian cell, comprising contacting the cell with a compound of Formula I. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo. In one embodiment, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof to a mammal having a cell having RET kinase activity. In some embodiments, the mammalian cell is a mammalian cancer cell. In one embodiment, the mammalian cancer cell is any cancer as described herein. In some embodiments, the mammalian cancer cell is a RET-associated cancer cell. In some embodiments, the mammalian cell is a gastrointestinal cell.

[00558] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" a RET kinase with a compound provided herein includes the administration of a compound provided herein to an individual or patient, such as a human, having a RET kinase, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the RET kinase.

[00559] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof, or a pharmaceutical composition thereof as defined herein

[00560] The phrase "effective amount" means an amount of compound that, when administered to a patient in need of such treatment, is sufficient to (i) treat a RET kinase-associated disease or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the patient in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

[00561] 4. Pharmaceutical compositions and administration

[00562] When employed as pharmaceuticals, the compound of Formula I-IV, including polymorph forms and pharmaceutically acceptable salts thereof, can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or can be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

[00563] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). For example, a pharmaceutical composition prepared using a compound of Formula I-IV or a pharmaceutically acceptable salt, amorphous, or polymorph form thereof. In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In some embodiments, the composition is formulated for

oral administration. In some embodiments, the composition is a solid oral formulation. In some embodiments, the composition is formulated as a tablet or capsule.

[00564] Further provided herein are pharmaceutical compositions containing a compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier. Pharmaceutical compositions containing a compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof as the active ingredient can be prepared by intimately mixing the compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending upon the desired route of administration (*e.g.*, oral, parenteral). In some embodiments, the composition is a solid oral composition.

[00565] Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers can be found in *The Handbook of Pharmaceutical Excipients*, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

[00566] Methods of formulating pharmaceutical compositions have been described in numerous publications such as *Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded*, Volumes 1-3, edited by Lieberman et al; *Pharmaceutical Dosage Forms: Parenteral Medications*, Volumes 1-2, edited by Avis et al; and *Pharmaceutical Dosage Forms: Disperse Systems*, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

[00567] In preparing the compositions in oral dosage form, any of the usual pharmaceutical media can be employed. Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Solid oral preparations can also be coated with substances such as sugars or be enteric-coated so as to

modulate major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients can be added to increase solubility or preservation. Injectable suspensions or solutions can also be prepared utilizing aqueous carriers along with appropriate additives. The pharmaceutical compositions herein will contain, per dosage unit, *e.g.*, tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described herein.

[00568] The compositions comprising a compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. The term “unit dosage form” refers to physically discrete units suitable as unitary dosages for human subjects and other patients, each unit containing a predetermined quantity of active material (*i.e.*, a compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof) calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[00569] In some embodiments, the compositions provided herein contain from about 5 mg to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 mg to about 10 mg, about 10 mg to about 15 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, or about 45 mg to about 50 mg of the active ingredient.

[00570] In some embodiments, the compositions provided herein contain from about 50 mg to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 mg to about 100 mg, about 100 mg to about 150 mg, about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 350 mg to about 400 mg, or about 450 mg to about 500 mg of the active ingredient. In some embodiments, the compositions provided herein contain about 10 mg, about 20 mg, about 80 mg, or about 160 mg of the active ingredient.

[00571] In some embodiments, the compositions provided herein contain from about 500 mg to about 1,000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, about 650 mg to about 700 mg, about 700

mg to about 750 mg, about 750 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, or about 950 mg to about 1,000 mg of the active ingredient.

[00572] The daily dosage of the compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof can be varied over a wide range from 1.0 to 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 160, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein. Preferably, the range is from about 0.5 to about 500 mg/kg of body weight per day, or any range therein. More preferably, from about 1.0 to about 250 mg/kg of body weight per day, or any range therein. More preferably, from about 0.1 to about 100 mg/kg of body weight per day, or any range therein. In an example, the range can be from about 0.1 to about 50.0 mg/kg of body weight per day, or any amount or range therein. In another example, the range can be from about 0.1 to about 15.0 mg/kg of body weight per day, or any range therein. In yet another example, the range can be from about 0.5 to about 7.5 mg/kg of body weight per day, or any amount to range therein. Pharmaceutical compositions containing a compound of Formula I-IV or a polymorph form or pharmaceutically acceptable salt thereof can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

[00573] The active compound may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. Optimal dosages to be administered can be readily determined by those skilled in the art. It will be understood, therefore, that the amount of the compound actually administered will usually be determined by a physician, and will vary according to the relevant circumstances, including the mode of administration, the actual compound administered, the strength of the preparation, the condition to be treated, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient response, age, weight, diet, time of administration and severity of the patient's symptoms, will result in the need to adjust dosages.

[00574] In some embodiments, the compounds provided herein can be administered in an amount ranging from about 1 mg/kg to about 100 mg/kg. In some embodiments, the compound

provided herein can be administered in an amount of about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 40 mg/kg, about 15 mg/kg to about 45 mg/kg, about 20 mg/kg to about 60 mg/kg, or about 40 mg/kg to about 70 mg/kg. For example, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, or about 100 mg/kg. In some embodiments, such administration can be once-daily or twice-daily (BID) administration.

[00575] In some embodiments, the compounds provided herein can be administered in an amount of about about 10 mg twice a day (BID), 20 mg BID, about 40 mg BID, about 60 mg BID, about 80 mg BID, about 120 mg BID, about 160 mg BID, and about 240 mg BID. In some embodiments, each dose is administered at least six hours after the previous dose. In some embodiments, each dose is administered at least twelve hours after the previous dose.

[00576] In some embodiments, a compound of Formula I-IV, or a polymorph form or pharmaceutically acceptable salt thereof exhibits pH dependent solubility at lower pH values. Accordingly, patients also receiving proton pump inhibitors (PPIs) and/or antacids may need to adjust the dosage of the compound of Formula I-IV, or a polymorph form or pharmaceutically acceptable salt thereof (e.g., increase the dose of the compound of Formula I-IV, or a polymorph form or pharmaceutically acceptable salt thereof). In some embodiments, the isoform of cytochrome P450 (CYP) that metabolizes a compound of Formula I-IV, or a polymorph form or pharmaceutically acceptable salt thereof, is CYP3A4. Accordingly, patients also receiving agents that inhibit or induce CYP3A4 may need to adjust the dosage of the compound of Formula I-IV, or a polymorph form or pharmaceutically acceptable salt thereof (e.g., increase the dose of the compound of Formula I-IV, or a polymorph form or pharmaceutically acceptable salt thereof, in the case of a CYP3A4 inducer or decrease the dose of the compound of Formula I-IV, or a polymorph form or pharmaceutically acceptable salt thereof, in the case of a CYP3A4 inhibitor).

[00577]

[00578] One skilled in the art will recognize that both *in vivo* and *in vitro* trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

[00579] One skilled in the art will further recognize that human clinical trials including first-in-

human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, can be completed according to methods well known in the clinical and medical arts.

[00580] 5. Kits

[00581] Provided herein are pharmaceutical kits useful, for example, in the treatment of RET-associated diseases or disorders, such as cancer or irritable bowel syndrome (IBS), which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

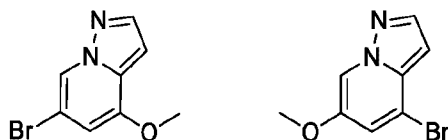
EXAMPLES

[00582] The following examples illustrate the invention.

[00583] EXAMPLE 1: Synthesis of the compound of Formula I

[00584] Intermediate A1 and A2

[00585] 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (**A1**) and 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (**A2**)



[00586] Part A: Preparation of O-(mesitylsulfonyl)hydroxylamine (Intermediate R1)

[00587] Step 1: Preparation of tert-butyl (mesitylsulfonyl)oxycarbamate. To a 0°C solution of 2,4,6-trimethylbenzene-1-sulfonyl chloride (10.0 g, 45.72 mmol) and tert-butyl hydroxycarbamate (6.088 g, 45.72 mmol) in MTBE (100 mL) was added TEA (14.46 mL, 48.01 mmol) dropwise while stirring. The resulting suspension was stirred at 0°C for an additional 30 min and then warmed to ambient temperature. The reaction was then diluted with water (100 mL) and adjusted to pH 4 with 1 N HCl_(aq). The organic layer was dried (Na₂SO₄), filtered, and concentrated to yield the title compound initially as a yellowish oil, which upon drying overnight under high vacuum

became a white solid (12.89 g, 89% yield). ^1H NMR (CDCl_3): δ 7.66 (br s, 1H), 6.98 (s, 2H), 2.67 (s, 6H), 2.32 (s, 3H), 1.31 (s, 9H).

[00588] Step 2: Preparation of O-(mesitylsulfonyl)hydroxylamine (Intermediate R1). To TFA (117 mL, 1521 mmol) at 0°C was slowly added tert-butyl (mesitylsulfonyl)oxycarbamate (39.0 g, 124 mmol) over 25 min. The reaction mixture was stirred at 0°C for 1.5 h and then quenched with the sequential addition of crushed ice and water. The resulting thick suspension was vigorously stirred at ambient temperature for 5 min. Without allowing the filter cake to run dry, the solids were collected by careful vacuum filtration, followed by subsequent rinsing with water (4 L) until the filtrate reached pH 6 (*Caution: explosion risk exists with dry compound at ambient temperature*). The wet filter cake was taken up in dichloromethane (150 mL) and the resulting biphasic solution was separated. The dichloromethane layer was dried over MgSO_4 for 30 min and then filtered and rinsed with dichloromethane (420 mL) to provide the title compound as a 0.22 M solution in dichloromethane.

[00589] **Part B:** Preparation of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (A1) and 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (A2)

[00590] Step 1: Preparation of 1-amino-3-bromo-5-methoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate. To a solution of O-(mesitylsulfonyl)hydroxylamine (Intermediate R1) (26.6 g, 117 mmol) in DCM (570 mL) cooled to 0°C was added 3-bromo-5-methoxypyridine (22.1 g, 117 mmol) in portions. The reaction mixture was stirred for 1 h at 0°C then treated with additional 3-bromo-5-methoxypyridine (250 mg, 1.39 mmol) and stirred for an additional 2 h at 0°C . The reaction mixture was diluted with Et_2O (600 mL), stirred at 0°C for 10 min and then vacuum filtered, rinsed with Et_2O (3×250 mL). Upon reduction in volume by about 1/3, the filtrate yielded additional precipitate which was collected by filtration. Both filter cakes were dried *in vacuo* to provide the title compound (39.3 g, 83% yield). ^1H NMR (CDCl_3) δ 9.25 (br s, 1H), 8.99 (m, 1H), 8.74 (m, 1H), 7.46 (m, 1H), 6.83 (s, 2H), 3.92 (s, 3H), 2.65 (s, 6H), 2.22 (s, 3H).

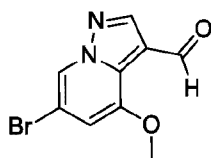
[00591] Step 2: Preparation of Ethyl 6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate and Ethyl 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carboxylate. To a magnetically stirred white suspension of 1-amino-3-bromo-5-methoxypyridin-1-ium 2,4,6-trimethylbenzenesulfonate (33.24 g, 82.42 mmol) in DMF (82 mL) at ambient temperature was added TEA (22.98 mL, 164.8 mmol), followed by drop-wise addition of ethyl propiolate (16.71 mL, 164.8 mmol). After vigorous stirring for 2 d, the reaction was slowly quenched via portion-

wise addition to rapidly stirring ice water (820 mL). The mixture was stirred at ambient temperature for 10 min and then vacuum filtered. Solids collected were rinsed with water and air-dried, yielding the title compounds as an orange solid in an isomeric ratio of about 4:1 (by ^1H NMR) with the 6-Br isomer as the major isomer (21 g). The wet solid isomeric mixture (about 75% w/w) was directly used in Step 3 without further purification. MS (apci) m/z = 298.9, 300.9 (M+H). Regioisomeric ratio was determined by MeO chemical shift in ^1H NMR (CDCl_3) δ 3.98 (6-Br isomer) vs. 3.83 (4-Br isomer).

[00592] Step 3: Preparation of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (A1) and 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (A2). The isomeric mixture of ethyl 6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate and ethyl 4-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate from Step 2 (15 g, 50.1 mmol) was added to 48% HBr (114 mL) while stirring, then heated at 80°C for 90 min followed by stirring at ambient temperature overnight. The resulting suspension was vacuum filtered and rinsed with water. The aqueous filtrate and the filter cake were treated independently. The filter cake was taken up in MTBE and vacuum filtered to remove insoluble impurities. The MTBE filtrate was dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to yield 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (Intermediate A1) as a beige solid (about 98:2 6-/4- Br; 5.08 g). MS (apci) m/z = 226.9, 228.9 (M+H). ^1H NMR (CDCl_3) δ 8.26 (m, 1H), 7.82 (d, 1H), 6.61 (m, 1H), 6.43 (m, 1H), 3.94 (s, 3H).

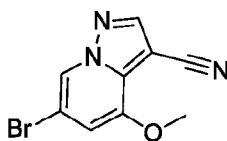
[00593] Independently the original aqueous reaction mixture filtrate was extracted with EtOAc (2×500 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was taken up in DCM (50 mL) and then filtered to remove insoluble solids. Concentration of the DCM filtrate under vacuum followed by silica chromatography (0 to 50% EtOAc/hexanes) yielded a second batch of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (Intermediate A1) as white solid (upper R_f spot, 2.06 g), as well as the minor isomer title compound 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (Intermediate A2) also as white solid (lower R_f spot, 1.32 g). MS (apci) m/z = 226.9, 228.9 (M+H). ^1H NMR (CDCl_3) δ 8.02 (m, 1H), 7.85 (d, 1H), 7.17 (d, 1H), 6.55 (m, 1H), 3.80 (s, 3H).

[00594] Intermediate A3



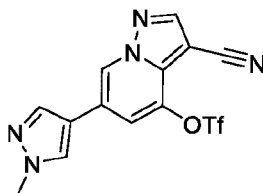
[00595] 6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde

[00596] To a 0°C solution of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (Intermediate A1, 0.75 g, 3.303 mmol) in DMF (33 mL) was slowly added POCl₃ (0.92 mL, 9.909 mmol). The reaction was warmed to ambient temperature and stirred for 4 h and then diluted with H₂O (30 mL). The resulting suspension was basified to pH 9-10 with 1 M NaOH_(aq), then stirred for 1 h and vacuum filtered, then rinsed sequentially with H₂O (25 mL) and MTBE (50 mL) to yield the title compound (0.76 g, 90% yield). MS (apci) m/z = 256.9 (M+H).

[00597] **Intermediate A4**

[00598] Step 1: Preparation of (E)-6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde oxime. To a suspension of 6-Bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde (Intermediate A3, 0.76 g, 3.0 mmol) and hydroxylamine hydrochloride (0.31 g, 4.5 mmol) in EtOH (40 mL) was added water (20 mL), and the reaction was stirred at 50°C for 4 h. After cooling to ambient temperature the reaction mixture was concentrated *in vacuo*. The residue was suspended in water, then treated with saturated NaHCO_{3(aq)} and vacuum filtered. The solids were rinsed sequentially with H₂O (25 mL) and MTBE (50 mL) to yield the title compound (0.68 g, 84% yield). MS (apci) m/z = 271.9 (M+H).

[00599] Step 2: Preparation of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile. A solution of (E)-6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde oxime (17.15 g, 63.50 mmol) in acetic anhydride (707 mL, 7.49 mol) was heated at 120°C overnight. Following subsequent distillation to remove the acetic anhydride, the remaining residue was dried *in vacuo* to yield the title compound (15.92 g, 99.4% yield). ¹H NMR (CDCl₃) δ 8.32 (m, 1H), 8.12 (s, 1H), 6.74 (m, 1H), 4.03 (s, 3H).

[00600] **Intermediate A5****[00601]** 3-cyano-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-4-yl

trifluoromethanesulfonate

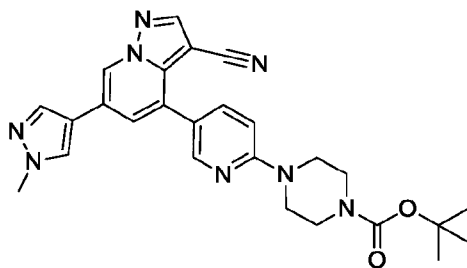
[00602] Step 1: Preparation of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a solution of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carbonitrile (Intermediate A4, 50 g, 198.4 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (49.53 g, 238.0 mmol) in dioxane (660 mL) was added 2 M Na₂CO_{3(aq)} (297.5 mL, 595.1 mmol). The reaction mixture was sparged with nitrogen for 20 min before Pd(PPh₃)₄ (4.584 g, 3.967 mmol) was introduced, followed by additional 5 min of sparging with nitrogen. The reaction was heated at 80°C for 18 h, then cooled to ambient temperature and vigorously stirred for 2 h. The suspension was vacuum filtered, rinsed sequentially with H₂O (2 × 300 mL) and MTBE (3 × 300 mL), then dried *in vacuo* overnight to yield the title compound, which was used in the next step without further purification (52.62 g). MS (apci), m/z = 254.1 (M+H).

[00603] Step 2: Preparation of 4-hydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. To a suspension of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (52.62 g, 207.8 mmol) in DCE (2 L) was added AlCl₃ (92.86 g, 696.42 mmol), and the reaction mixture was stirred at 80°C for 3 h. Additional AlCl₃ (2.5 g, 18.75 mmol) was introduced and the reaction was refluxed overnight. After cooling to ambient temperature the reaction mixture was diluted with DCE (1 L) and then quenched with portions of H₂O (5 × 500 mL). The mixture was stirred at ambient temperature for 3 h before the resulting suspension was vacuum filtered and the filter cake dried in a vacuum oven (40°C) to afford the title compound, which was used in the next step without further purification (43.69 g). MS (apci) m/z = 239.9 (M+H). ¹H NMR (d⁶-DMSO) δ 11.38 (s, 1H), 8.74 (d, 1H), 8.50 (s, 1H), 8.21 (s, 1H), 7.94 (s, 1H), 6.96 (d, 1H), 3.88 (s, 3H).

[00604] Step 3: Preparation of 3-cyano-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-4-yl trifluoromethanesulfonate. To a suspension of 4-hydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile (43.69 g, 182.6 mmol) in DMA (365 mL) was added DIEA (63.6 mL, 365.3 mmol) followed by 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (71.77 g, 200.9 mmol). The resulting solution was stirred at ambient temperature for 2 h and then slowly poured into H₂O (4 L). The resulting suspension was stirred for 2 h then vacuum filtered. The filter cake was rinsed with H₂O (3 × 500 mL) and air dried overnight. The filter cake was then dissolved in DCM (1.6 L) and the resulting

biphasic mixture was phase-separated. The organic layer was dried over anhydrous MgSO_4 , filtered through Celite[®] and rinsed with DCM. The combined organic layers were concentrated to yield the title compound as a 90% pure tan solid (64.3 g, 95% yield). The purity of the title compound can be further improved to >95% via silica chromatography (0-90% acetone/hexanes). ^{19}F NMR (CDCl_3) δ -72.0. ^1H NMR (CDCl_3) δ 8.66 (d, 1H), 8.29 (s, 1H), 7.77 (d, 1H), 7.70 (s, 1H), 7.55 (d, 1H), 4.01 (s, 3H).

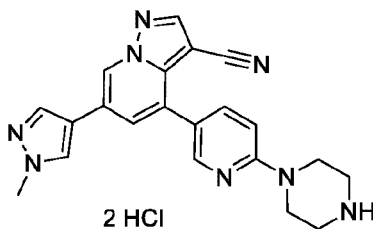
[00605] Intermediate A6



[00606] tert-butyl 4-(5-(3-cyano-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperazine-1-carboxylate.

[00607] To a mixture of 3-cyano-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-4-yl trifluoromethanesulfonate (Intermediate **A5**; 10.0 g, 26.9 mmol) and tert-butyl 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine-1-carboxylate (12.6 g, 32.3 mmol) in dioxane (250 mL) was added 2 M $\text{Na}_2\text{CO}_3(\text{aq})$ (14.3 g, 135 mmol), and the reaction mixture was sparged with nitrogen for 15 min before introducing $\text{Pd}_2(\text{dba})_3$ (1.23 g, 1.35 mmol) and X-Phos (2.57 g, 5.39 mmol). The mixture was sparged with nitrogen for an additional 5 min and then heated at 80°C overnight. After cooling to ambient temperature, the reaction mixture was poured into H_2O (1.5 L) and stirred for 2 h. The resulting suspension was filtered and rinsed sequentially with H_2O (3×200 mL), MTBE (4×100 mL) and hexanes (4×100 mL), yielding the title compound as a solid after drying *in vacuo* overnight (12 g, 92% yield). MS (apci) m/z = 485.2 (M+H).

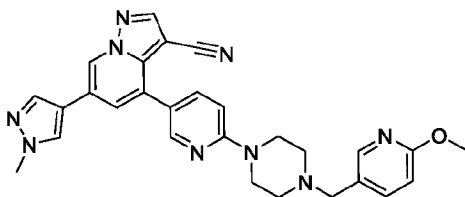
[00608] Intermediate A7



[00609] 6-(1-methyl-1H-pyrazol-4-yl)-4-(6-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride

[00610] To a solution of tert-butyl 4-(5-(3-cyano-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-4-yl)pyridin-2-yl)piperazine-1-carboxylate (**A6**, 12.0 g, 24.77 mmol) in MeOH (12 mL) and DCM (50 mL) was added HCl (5-6M in iPrOH, 49.53 mL, 247.7 mmol). After stirring at ambient temperature for 21 h the reaction was diluted with MeOH (50 mL) and DCM (50 mL). The suspension was stirred at ambient temperature until LCMS indicated the reaction was complete. The reaction mixture was filtered, rinsed with Et₂O (5 × 50 mL) and then dried for 19 h in a 45°C vacuum oven to yield the title compound (9.97 g, 88% yield). MS (apci) m/z = 385.1 (M+H).

[00611] **Compound of Formula I**



[00612] 4-(6-(4-((6-methoxypyridin-3-yl)methyl)piperazin-1-yl)pyridin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

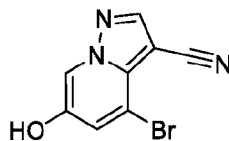
[00613] Procedure 1: A room temperature solution of 6-(1-methyl-1H-pyrazol-4-yl)-4-(6-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile dihydrochloride (**A7**; 0.125 g, 0.273 mmol) in dry DMA (2.5 mL) was treated with TEA (114 µL, 0.820 mmol), Me₄N(AcO)₃BH (144 mg, 0.547 mmol) and 6-methoxynicotinaldehyde (0.0750 g, 0.547 mmol). The resulting mixture was stirred overnight at room temperature, then quenched with water and CHCl₃ and allowed to stir for 30 min. The resulting biphasic mixture was filtered through a PS frit, and the aqueous layer was washed with CHCl₃. The organic filtrate was concentrated *in vacuo*, and the residue was purified by C18 reverse-phase chromatography (5-90% ACN/water as the gradient eluent) to afford the title compound (56 mg, 41% yield). MS (apci) m/z = 506.0 (M+H).

[00614] Procedure 2: To a reaction vessel was charged 6-(1-methyl-1H-pyrazol-4-yl)-4-(6-(piperazin-1-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile tetrahydrochloride (**A7**; 19.0 g), and 6-methoxynicotinaldehyde (7.37 g). DMSO (247 mL) was added followed by triethylamine (15 mL). The yellow slurry stirred at room temperature for ~2.5 hours and then sodium triacetoxyborohydride (15.2 g) was added in one portion and the reaction was heated to

30°C and stirred overnight. The reaction was judged complete by HPLC and the mixture was cooled in an ice/water bath to 19°C. Water (550 mL) was added slowly, keeping the temperature below 30°C. The suspension stirred for 3.5 hours and was then filtered and the cake was washed with water (2 x 285 mL). The solid was dried in a vacuum oven at 45°C to produce the title compound (18.0 g, 99.4%). The crystalline solid was analyzed by XRPD producing a diffraction pattern consistent with Formula I form A.

[00615] EXAMPLE 2: Synthesis of compounds of Formula II-IV

[00616] Intermediate B1



[00617] 4-Bromo-6-hydroxypyrazolo[1,5-a]pyridine-3-carbonitrile

[00618] Step 1: Preparation of 1-amino-3-bromo-5-methoxypyridin-1-ium-2,4,6-trimethylbenzenesulfonate. To a solution of O-(mesitylsulfonyl)hydroxylamine (Intermediate **R1**, 26.6 g, 117 mmol) in dichloromethane (570 mL) cooled to 0°C was added 3-bromo-5-methoxypyridine (22.1 g, 117 mmol) in portions. The reaction mixture was stirred for 1 h at 0°C then treated with additional 3-bromo-5-methoxypyridine (250 mg, 1.39 mmol) and stirred for an additional 2 h at 0°C. The reaction mixture was diluted with Et₂O (600 mL), stirred at 0°C for 10 min and then vacuum filtered, and rinsed with Et₂O (3 x 250 mL). Upon reduction in volume by about 1/3, the filtrate yielded additional precipitate which was collected by filtration. Both filter cakes were dried *in vacuo* to provide the title compound (39.3 g, 83% yield). ¹H NMR (CDCl₃): δ 9.25 (br s, 1H), 8.99 (m, 1H), 8.74 (m, 1H), 7.46 (m, 1H), 6.83 (s, 2H), 3.92 (s, 3H), 2.65 (s, 6H), 2.22 (s, 3H).

[00619] Step 2: Preparation of ethyl-6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate and ethyl-4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carboxylate. To a magnetically stirred white suspension of 1-amino-3-bromo-5-methoxypyridin-1-ium-2,4,6-trimethylbenzenesulfonate (33.24 g, 82.42 mmol) in DMF (82 mL) at ambient temperature was added TEA (22.98 mL, 164.8 mmol), followed by dropwise addition of ethyl propiolate (16.71 mL, 164.8 mmol). After vigorous stirring for 2 d, the reaction was slowly quenched via portion-wise addition to rapidly stirring ice water (820 mL). The mixture was stirred at ambient

temperature for 10 min and then vacuum filtered. Solids collected were rinsed with water and air-dried, yielding the title compounds as an orange solid in an isomeric ratio of about 4:1 (by ^1H NMR) with the 6-Br isomer as the major isomer (21 g). The wet solid isomeric mixture (about 75% w/w) was directly used in Step 3 without further purification. MS (apci) m/z = 298.9, 300.9 (M+H). Regioisomeric ratio was determined by MeO chemical shift in ^1H NMR (CDCl_3) δ 3.98 (6-Br isomer) vs. 3.83 (4-Br isomer).

[00620] Step 3: Preparation of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (Intermediate B1) and 4-bromo-6-methoxypyrazolo[1,5-a]pyridine. The isomeric mixture of ethyl-6-bromo-4-methoxypyrazolo[1,5-a]pyridine-3-carboxylate and ethyl-4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carboxylate from Step 2 (15 g, 50.1 mmol) was added to 48% HBr (114 mL) while stirring, then heated at 80°C for 90 min, followed by stirring at ambient temperature overnight. The resulting suspension was vacuum filtered and rinsed with water. The aqueous filtrate and the filter cake were treated independently. The filter cake was taken up in MTBE and vacuum filtered to remove insoluble impurities. The MTBE filtrate was dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to yield 6-bromo-4-methoxypyrazolo[1,5-a]pyridine as a beige solid (about 98:2 6-/4- Br; 5.08 g). MS (apci) m/z = 226.9, 228.9 (M+H). ^1H NMR (CDCl_3): δ 8.26 (m, 1H), 7.82 (d, 1H), 6.61 (m, 1H), 6.43 (m, 1H), 3.94 (s, 3H). Independently, the original aqueous reaction mixture filtrate was extracted with EtOAc (2 $\times$ 500 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was taken up in DCM (50 mL) and then filtered to remove insoluble solids. Concentration of the DCM filtrate under vacuum followed by silica chromatography (0 to 50% EtOAc/hexanes) yielded a second batch of 6-bromo-4-methoxypyrazolo[1,5-a]pyridine (Intermediate 1) as a white solid (upper R_f spot, 2.06 g), as well as the minor isomer title compound 4-bromo-6-methoxypyrazolo[1,5-a]pyridine also as a white solid (lower R_f spot, 1.32 g). MS (apci) m/z = 226.9, 228.9 (M+H). ^1H NMR (CDCl_3): δ 8.02 (m, 1H), 7.85 (d, 1H), 7.17 (d, 1H), 6.55 (m, 1H), 3.80 (s, 3H).

[00621] Step 4: Preparation of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine-3-carbaldehyde: A solution of 4-bromo-6-methoxypyrazolo[1,5-a]pyridine (5.0 g, 22 mmol) in DMF (220 mL) was cooled to 0°C and then slowly treated with POCl_3 (6.2 mL, 66 mmol). The reaction was warmed to ambient temperature and stirred overnight. The reaction mixture was cooled to 0°C, quenched with water (220 mL), and basified with 6 M $\text{NaOH}_{(\text{aq})}$ to pH 9-10. The reaction mixture was stirred for 1 h and then vacuum filtered. The solids were rinsed sequentially with water (3 $\times$ 50 mL) and

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 276

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 276

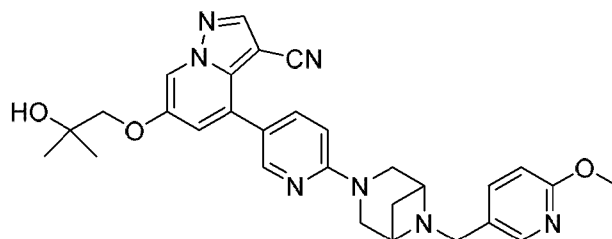
NOTE: For additional volumes, please contact the Canadian Patent Office

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NOTE POUR LE TOME / VOLUME NOTE:

What is claimed is:

1. A crystalline form of a compound of Formula II having the formula



wherein the crystalline form is selected from the group consisting of Form 1, Form 2, Form 7, and Form 8; wherein

Form 1 is characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 16.5 ± 0.2 , 18.9 ± 0.2 , and 26.0 ± 0.2 ;

Form 2 is characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 15.1 ± 0.2 , 17.8 ± 0.2 , and 24.2 ± 0.2 ;

Form 7 is characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 16.6 ± 0.2 , 18.0 ± 0.2 , and 19.9 ± 0.2 ; and

Form 8 is an isopropyl alcohol solvate of the compound of Formula II, and characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of 15.1 ± 0.2 , 17.8 ± 0.2 , and 24.2 ± 0.2 .

2. The crystalline form of claim 1, wherein the crystalline form is Form 1, characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 2θ values of:

- a) 16.5 ± 0.2 , 18.9 ± 0.2 , and 26.0 ± 0.2 ;
- b) 16.5 ± 0.2 , 18.9 ± 0.2 , 23.8 ± 0.2 , 25.3 ± 0.2 , and 26.0 ± 0.2 ;
- c) 16.5 ± 0.2 , 17.8 ± 0.2 , 18.9 ± 0.2 , 23.8 ± 0.2 , 25.3 ± 0.2 , 25.6 ± 0.2 , 26.0 ± 0.2 , and 28.3 ± 0.2 ; or
- d) 9.8 ± 0.2 , 16.5 ± 0.2 , 17.8 ± 0.2 , 18.9 ± 0.2 , 23.8 ± 0.2 , 25.0 ± 0.2 , 25.3 ± 0.2 , 25.6 ± 0.2 , 26.0 ± 0.2 , and 28.3 ± 0.2 .

3. A solid oral pharmaceutical composition comprising a pharmaceutically acceptable carrier and a crystalline form according to claim 1.

4. The crystalline form of claim 1, wherein the crystalline form is Form 2, characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at $^{\circ}2\theta$ values of:

- a) 15.1 ± 0.2 , 17.8 ± 0.2 , and 24.2 ± 0.2 ;
- b) 15.1 ± 0.2 , 17.8 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , and 24.2 ± 0.2 ;
- c) 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , and 24.6 ± 0.2 ; or
- d) 6.2 ± 0.2 , 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , 24.6 ± 0.2 , and 31.2 ± 0.2 .

5. The crystalline form of claim 1, wherein the crystalline form is Form 7, characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at $^{\circ}2\theta$ values of:

- a) 16.6 ± 0.2 , 18.0 ± 0.2 , and 19.9 ± 0.2 ;
- b) 16.6 ± 0.2 , 18.0 ± 0.2 , 19.3 ± 0.2 , 19.9 ± 0.2 , and 23.3 ± 0.2 ;
- c) 16.6 ± 0.2 , 17.3 ± 0.2 , 18.0 ± 0.2 , 19.0 ± 0.2 , 19.3 ± 0.2 , 19.9 ± 0.2 , 23.3 ± 0.2 , and 25.1 ± 0.2 ; or
- d) 15.8 ± 0.2 , 16.6 ± 0.2 , 17.3 ± 0.2 , 18.0 ± 0.2 , 19.0 ± 0.2 , 19.3 ± 0.2 , 19.9 ± 0.2 , 21.4 ± 0.2 , 23.3 ± 0.2 , and 25.1 ± 0.2 .

6. The crystalline form of claim 1, wherein the crystalline form is an isopropyl alcohol solvate Form 8, characterized by having an X-ray powder diffraction (XRPD) pattern comprising peaks at $^{\circ}2\theta$ values of:

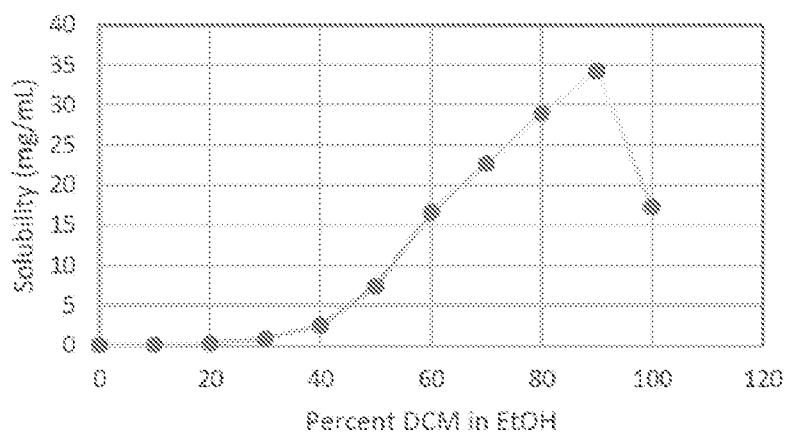
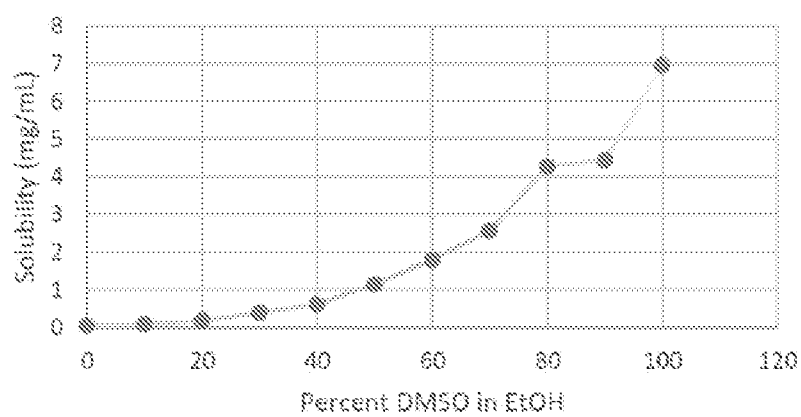
- a) 15.1 ± 0.2 , 17.8 ± 0.2 , and 24.2 ± 0.2 ;
- b) 15.1 ± 0.2 , 17.8 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , and 24.2 ± 0.2 ;
- c) 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , and 24.6 ± 0.2 ; or
- d) 6.2 ± 0.2 , 15.1 ± 0.2 , 17.8 ± 0.2 , 18.1 ± 0.2 , 20.4 ± 0.2 , 21.1 ± 0.2 , 23.4 ± 0.2 , 24.2 ± 0.2 , 24.6 ± 0.2 , and 31.2 ± 0.2 .

7. The pharmaceutical composition of claim 3, wherein the crystalline form of the compound of Formula II is Form 1 and the composition contains less than 15% by wt. of other forms of the compound.

8. The pharmaceutical composition of claim 3, wherein the crystalline form of the compound of Formula II is Form 2 and the composition contains less than 15% by wt. of other forms of the compound.

9. The pharmaceutical composition of claim 3, wherein the crystalline form of the compound of Formula II is Form 7 and the composition contains less than 15% by wt. of other forms of the compound.

10. The pharmaceutical composition of claim 3, wherein the crystalline form of the compound of Formula II is Form 8 and the composition contains less than 15% by wt. of other forms of the compound.

**Fig. 1A****Fig. 1B**

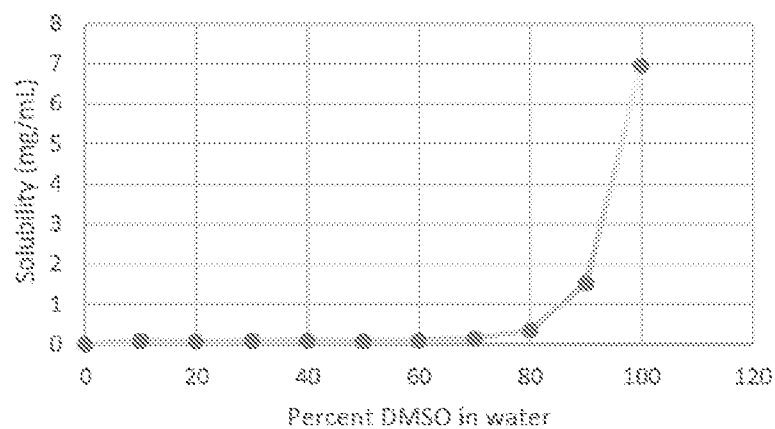


Fig. 1C

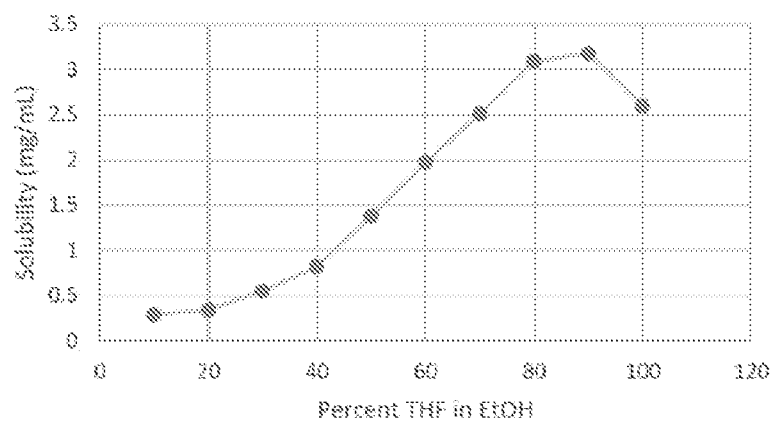
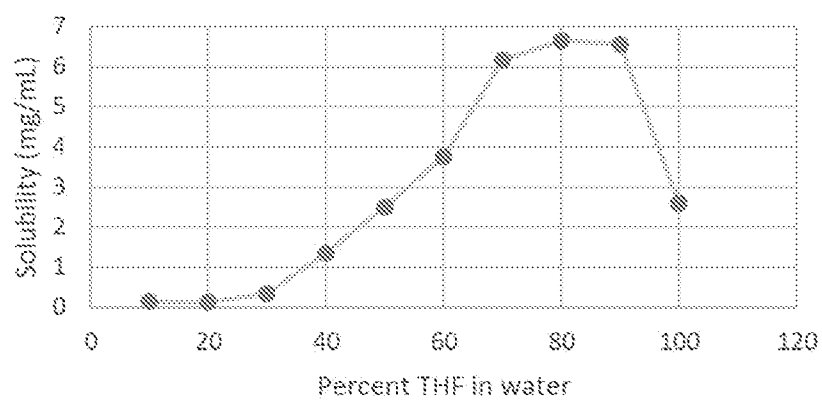


Fig. 1D

**Fig. 1E**

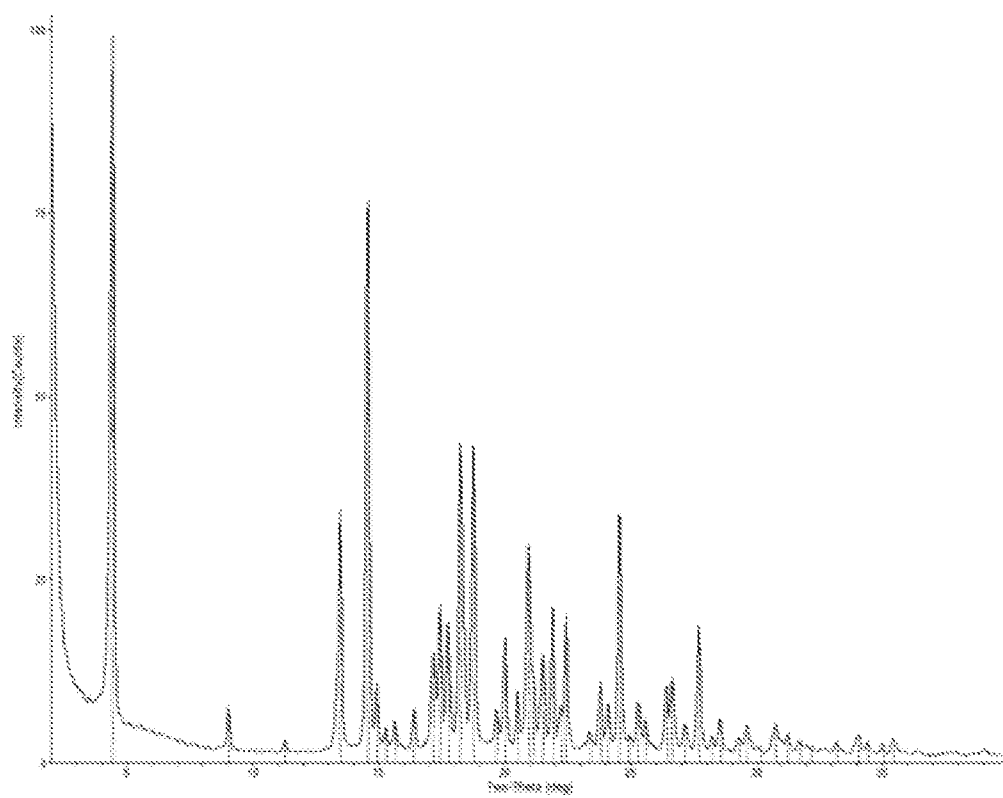


Fig. 2A

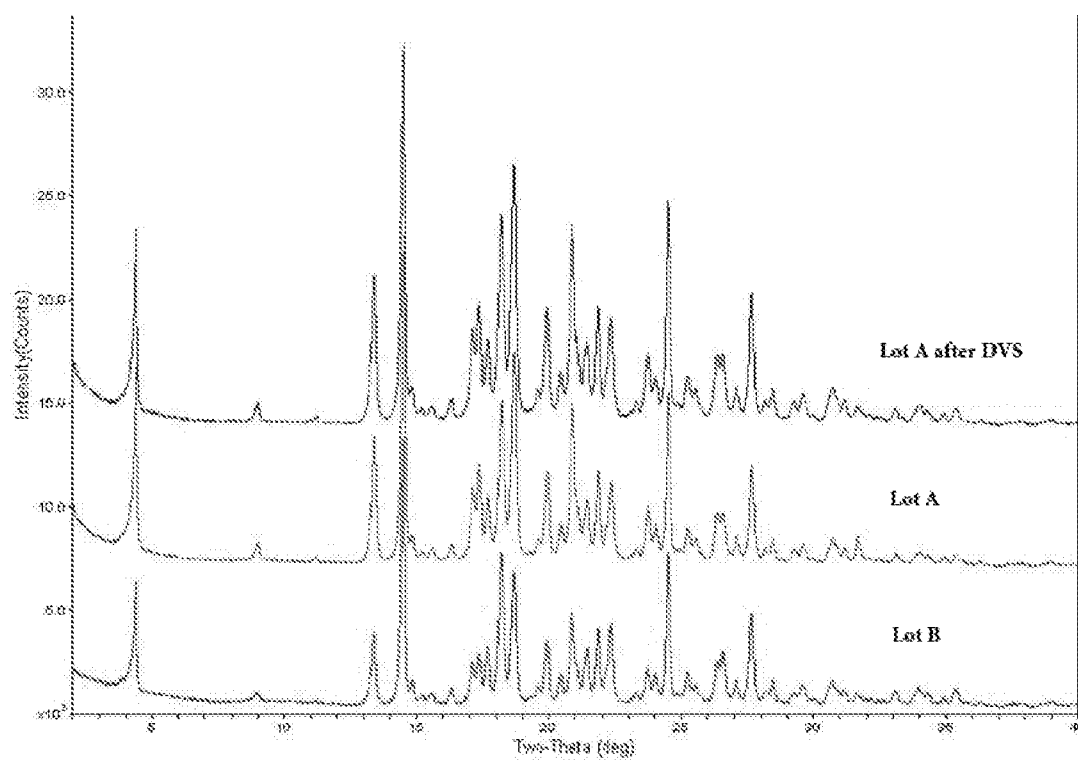


Fig. 2B

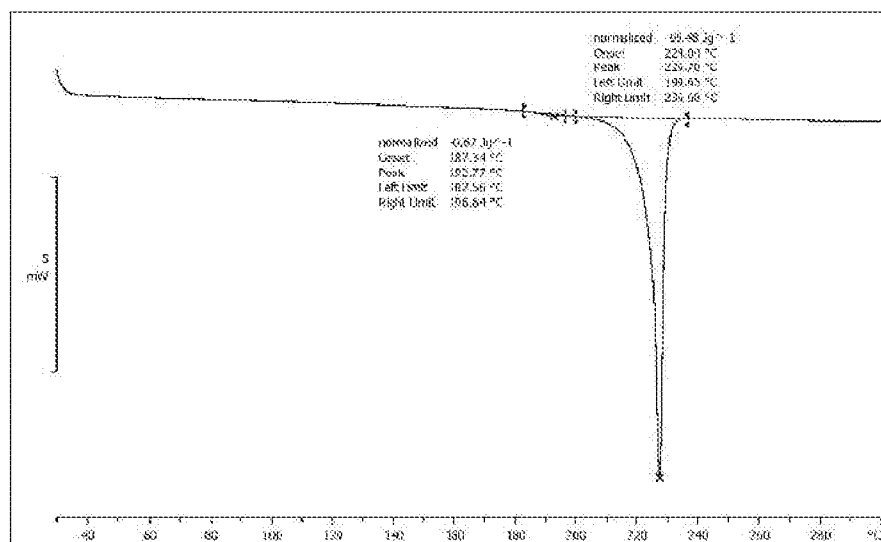


Fig. 2C

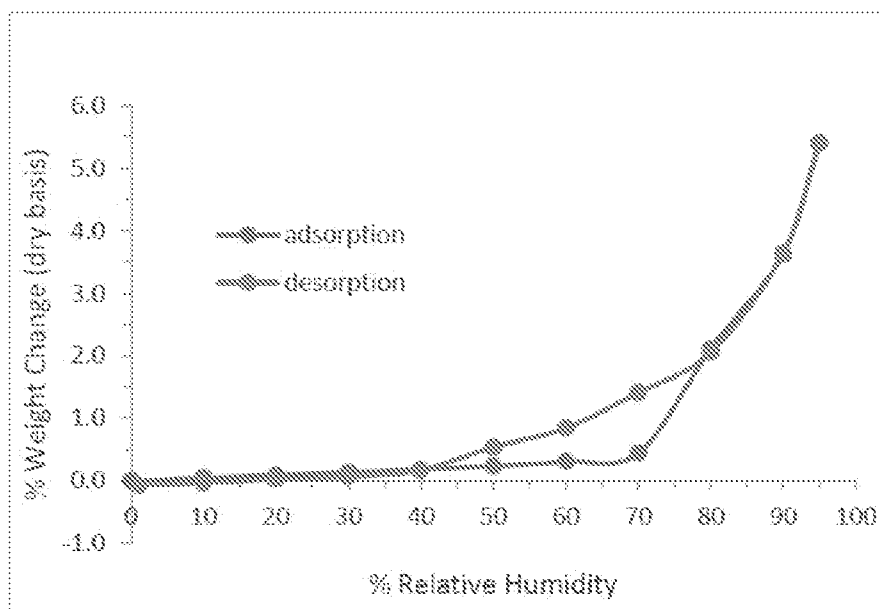


Fig. 2D

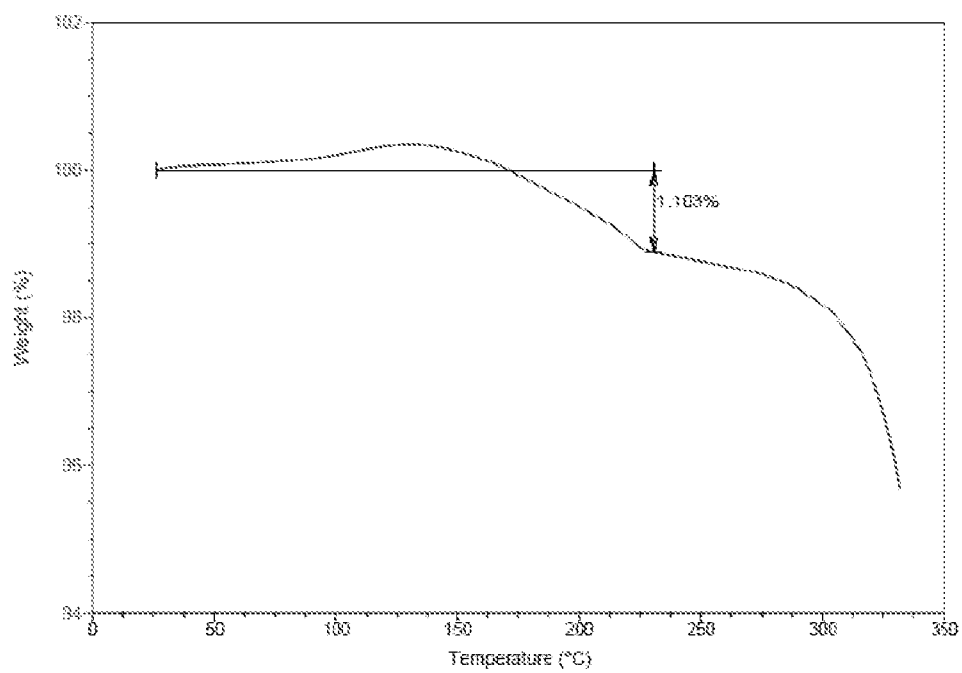


Fig. 2E

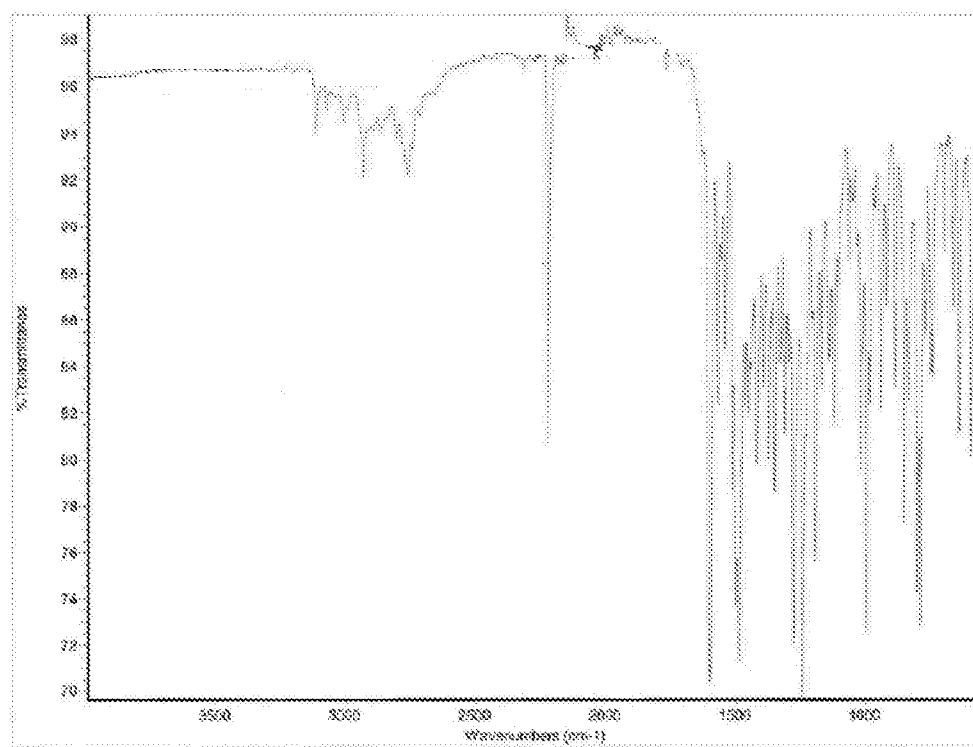


Fig. 2F

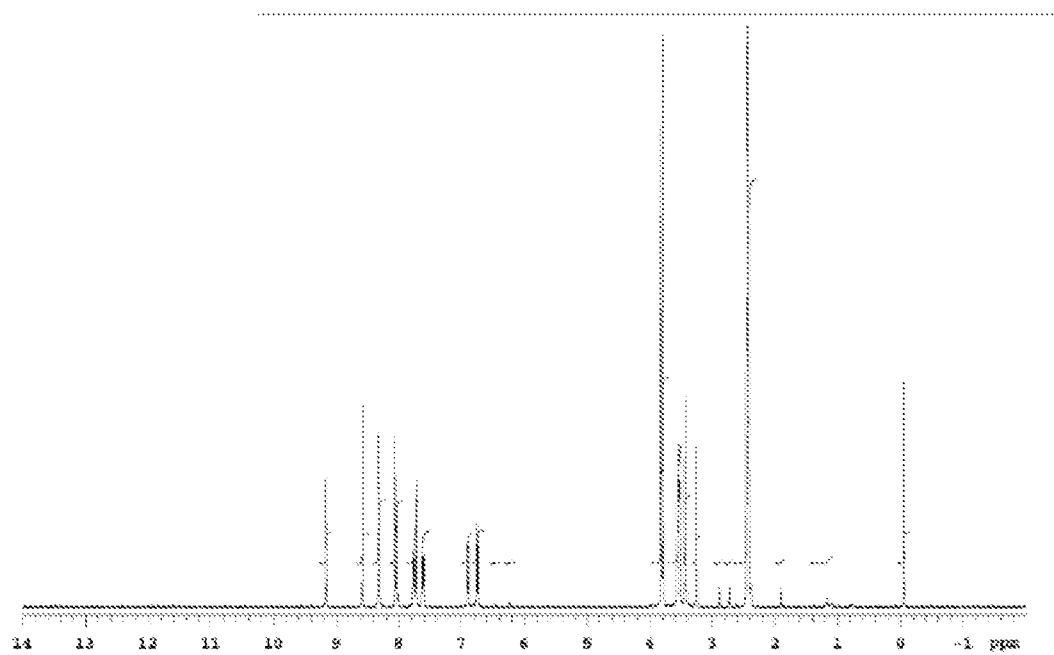


Fig. 2G

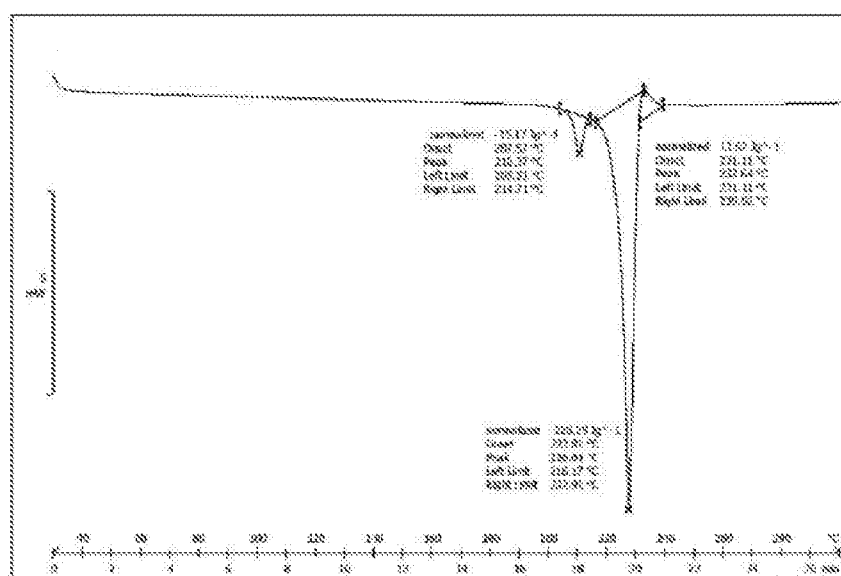


Fig. 3

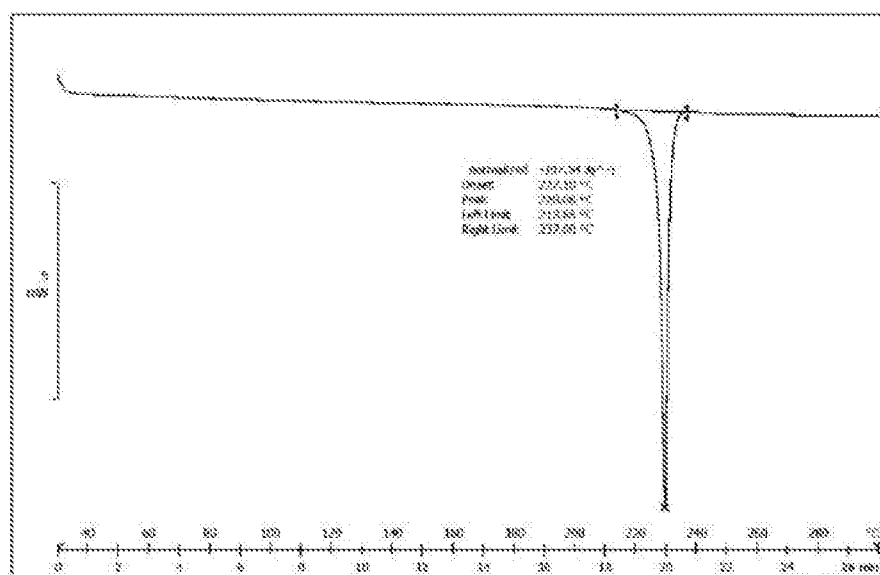


Fig. 4

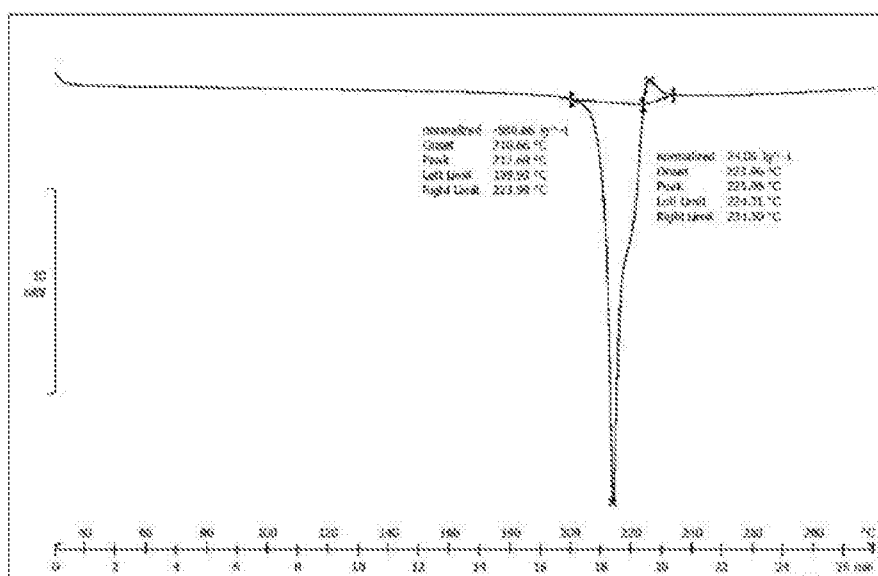


Fig. 5

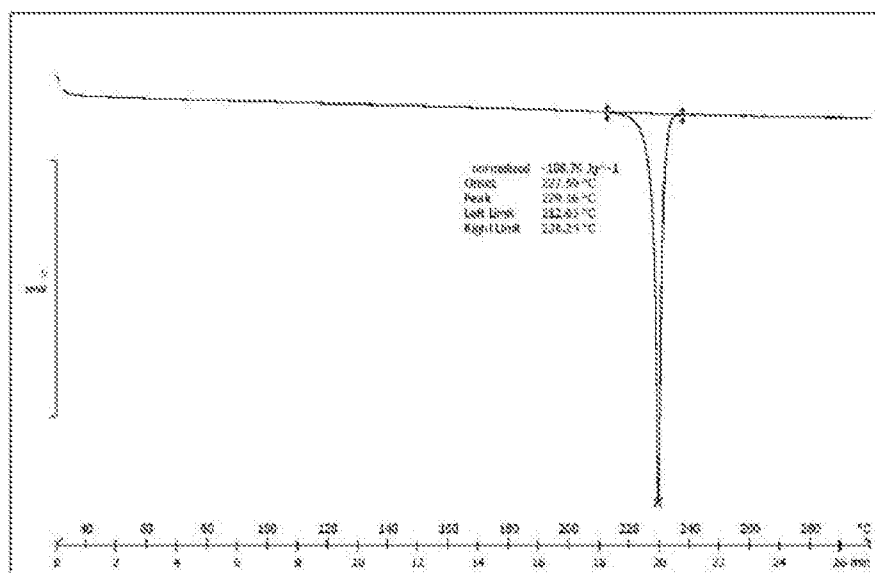


Fig. 6

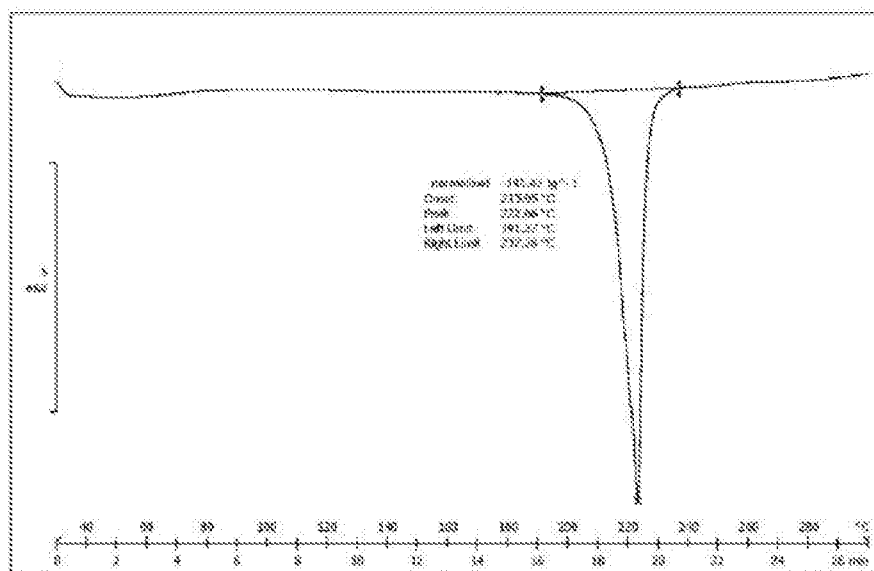


Fig. 7

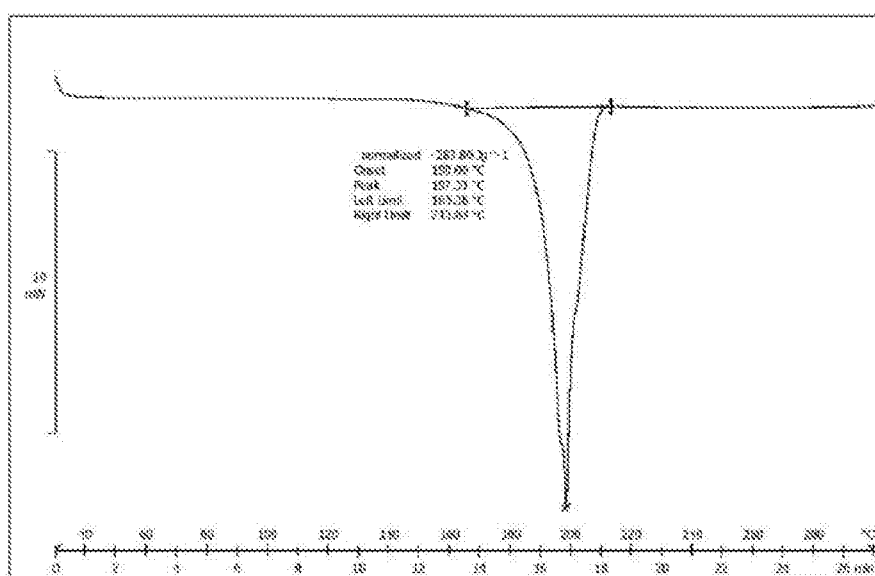


Fig. 8

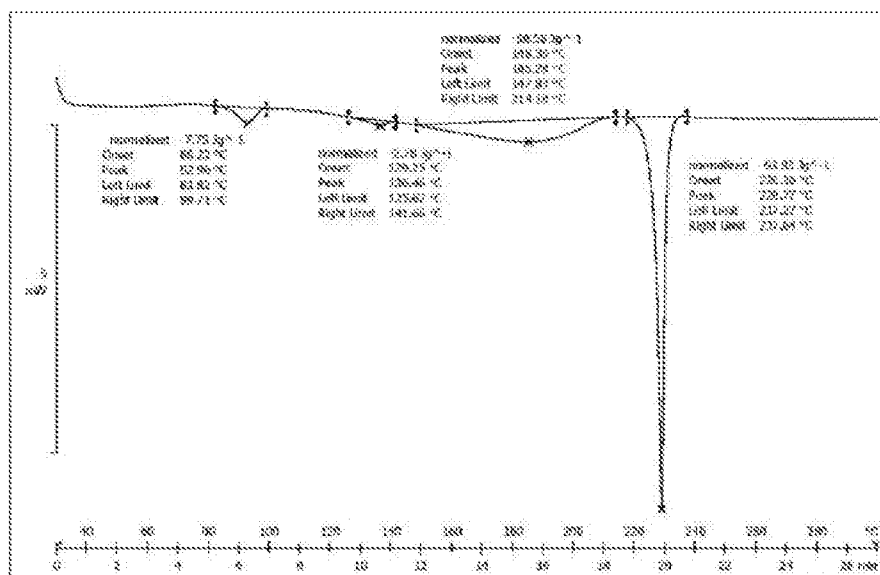


Fig. 9

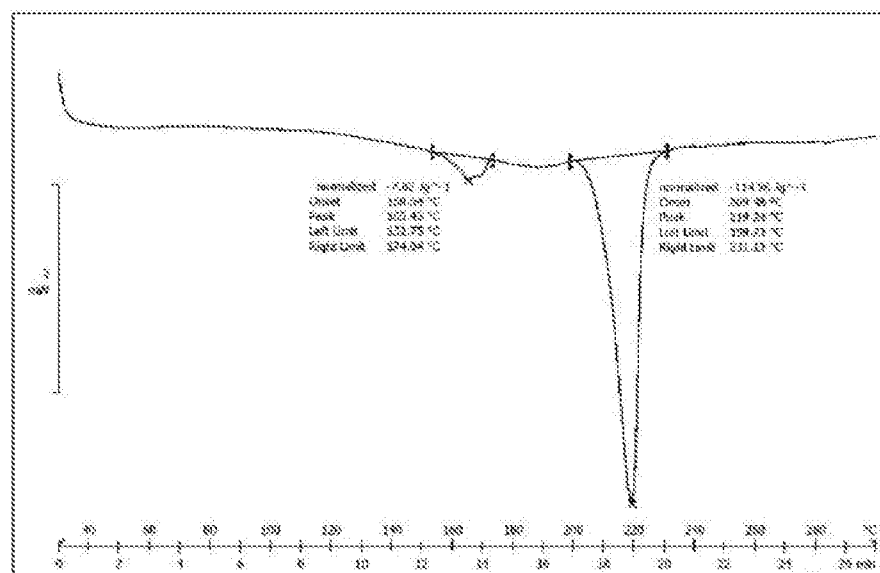


Fig. 10

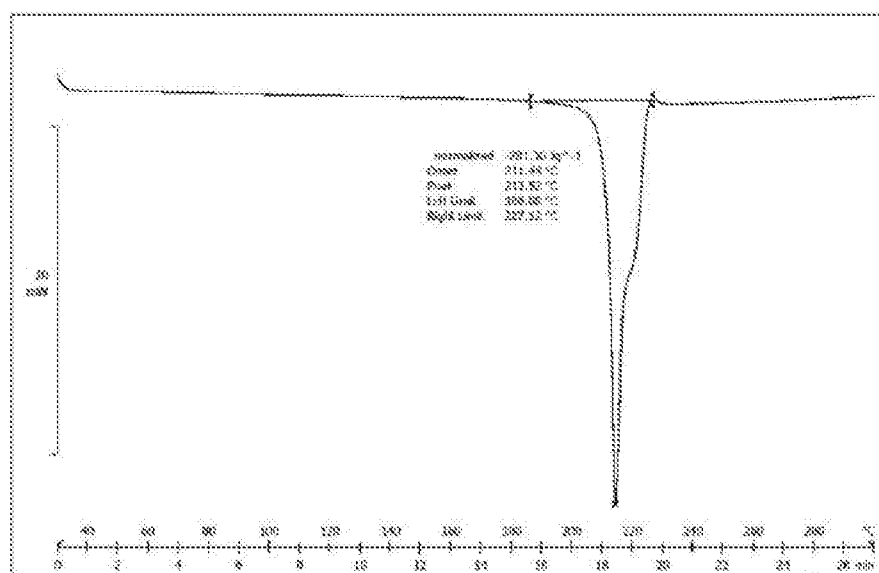


Fig. 11

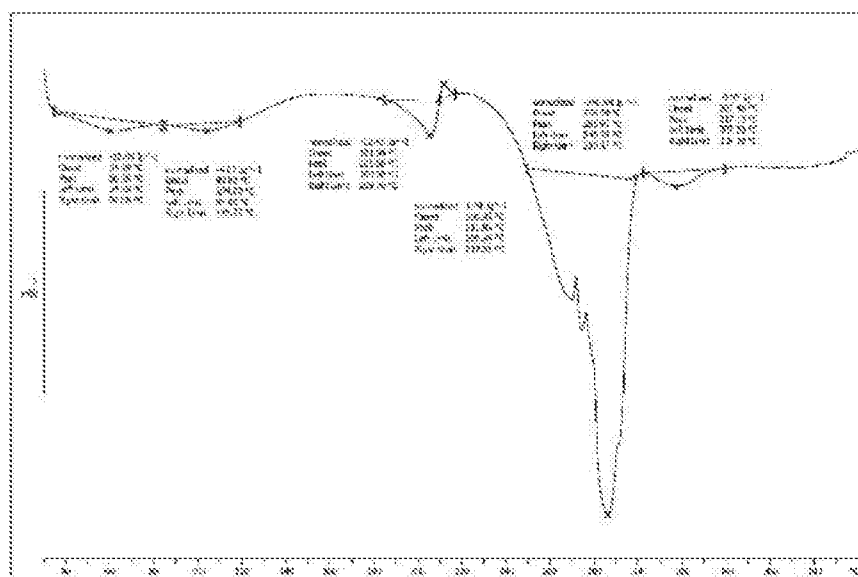


Fig. 12

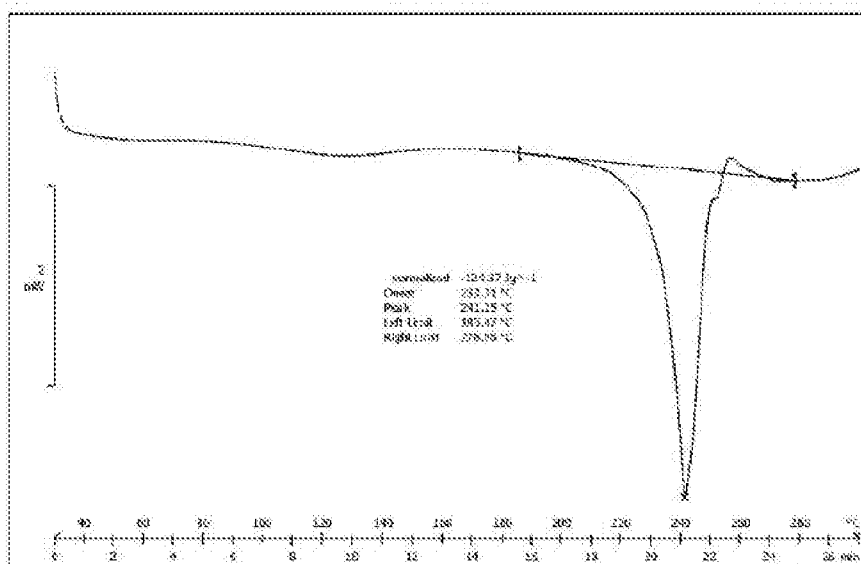


Fig. 13

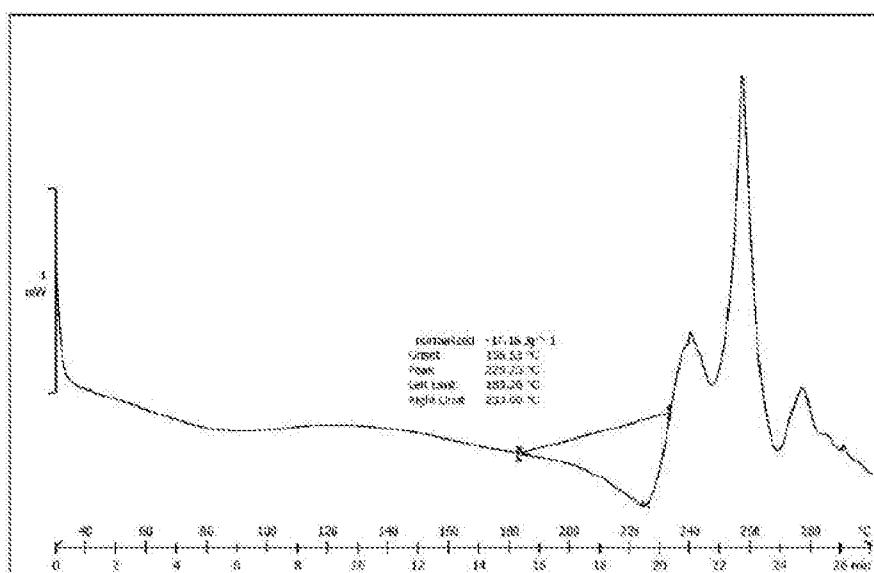


Fig. 14

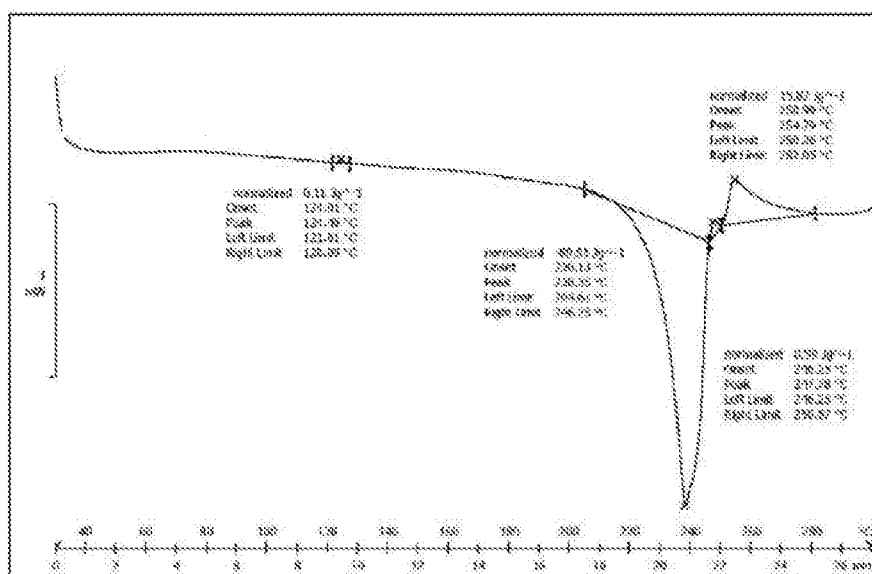


Fig. 15A

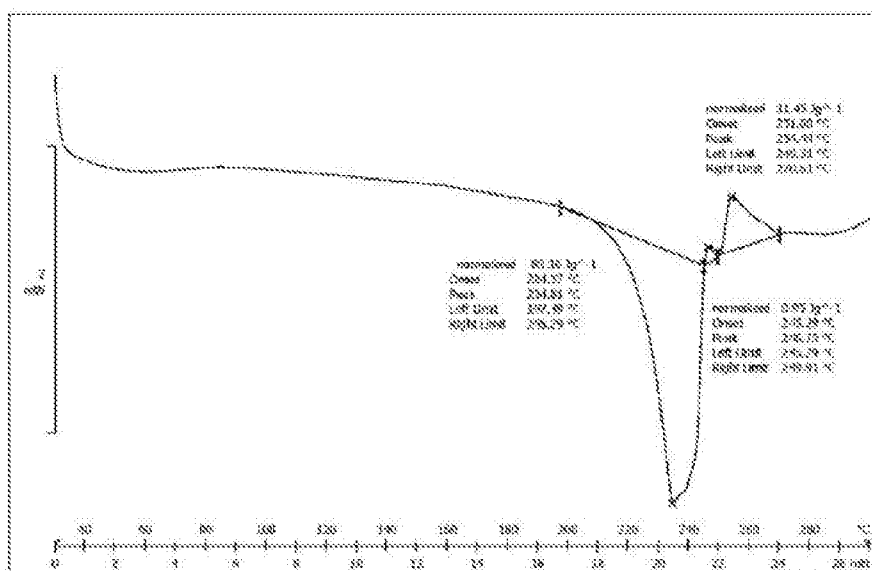
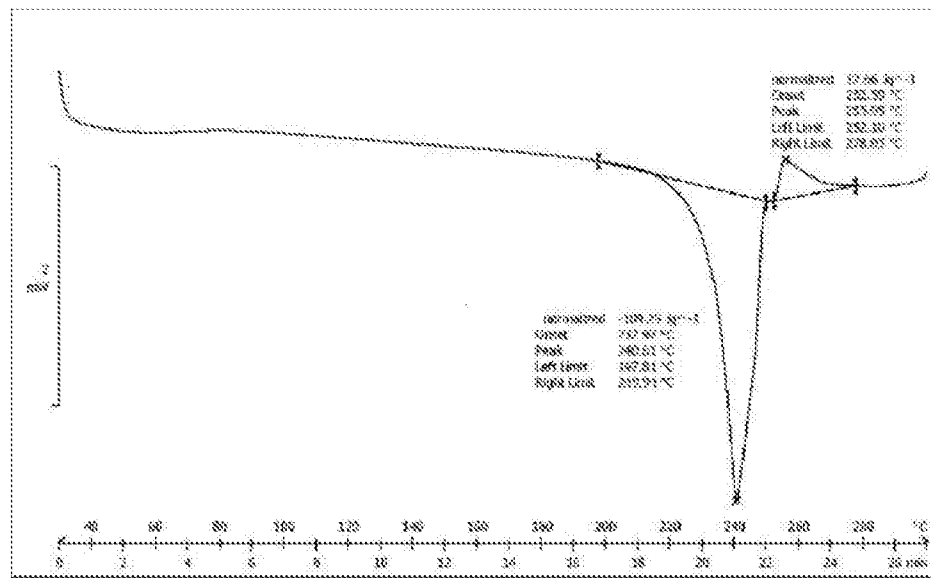


Fig. 15B



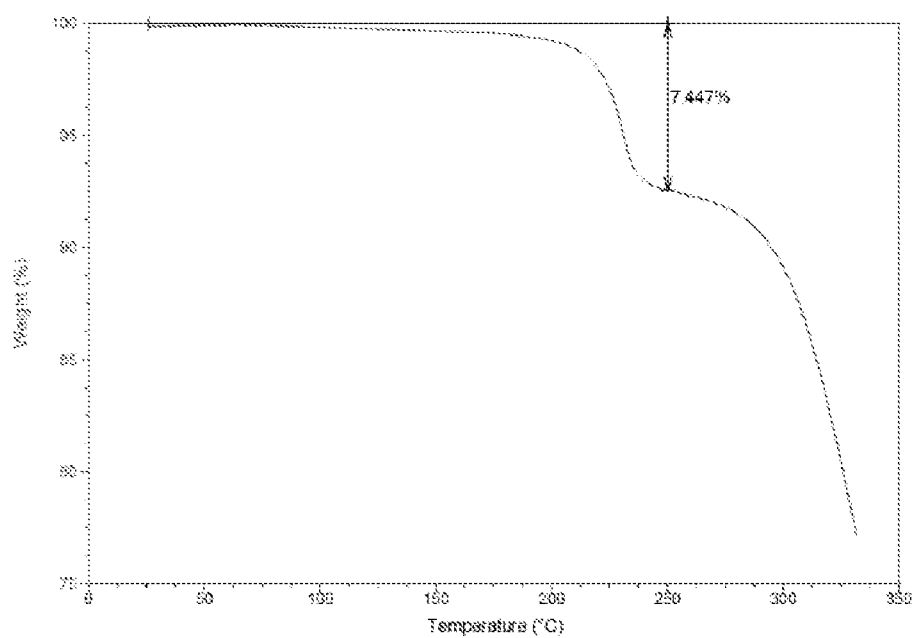


Fig. 16C

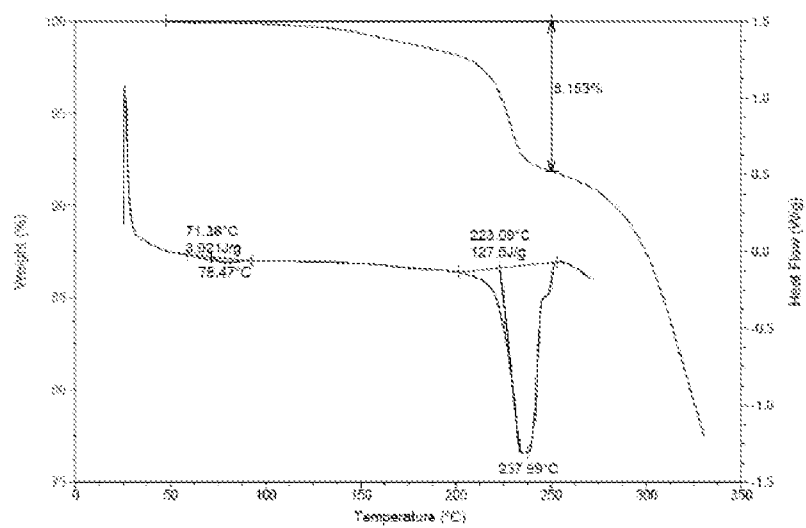


Fig. 16D

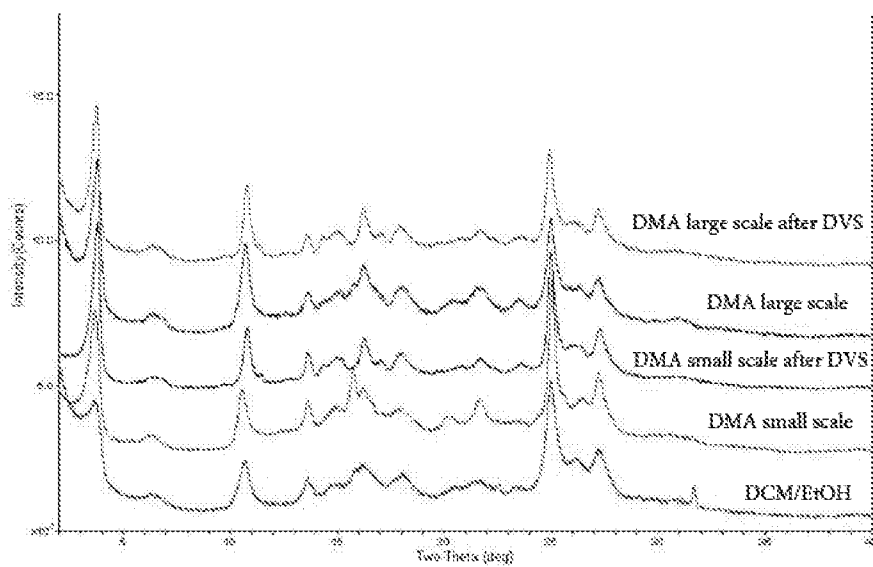


Fig. 16E

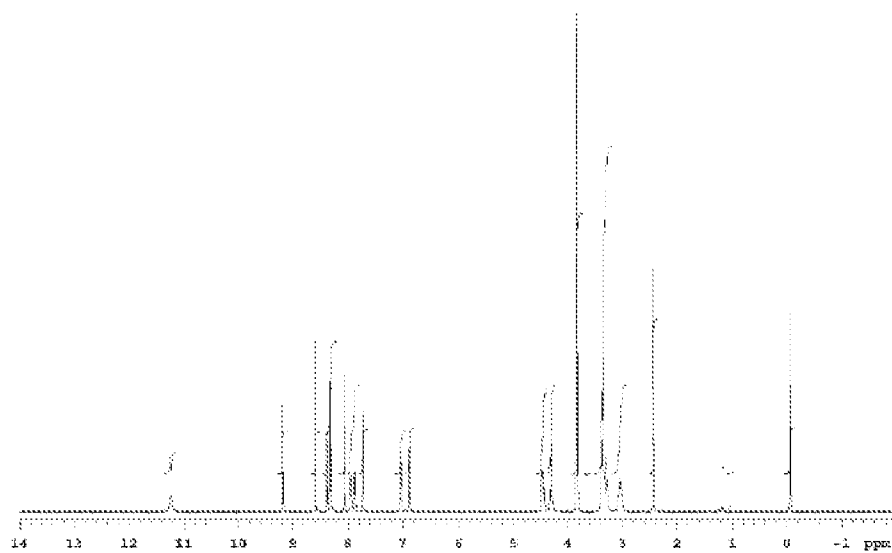


Fig. 16F

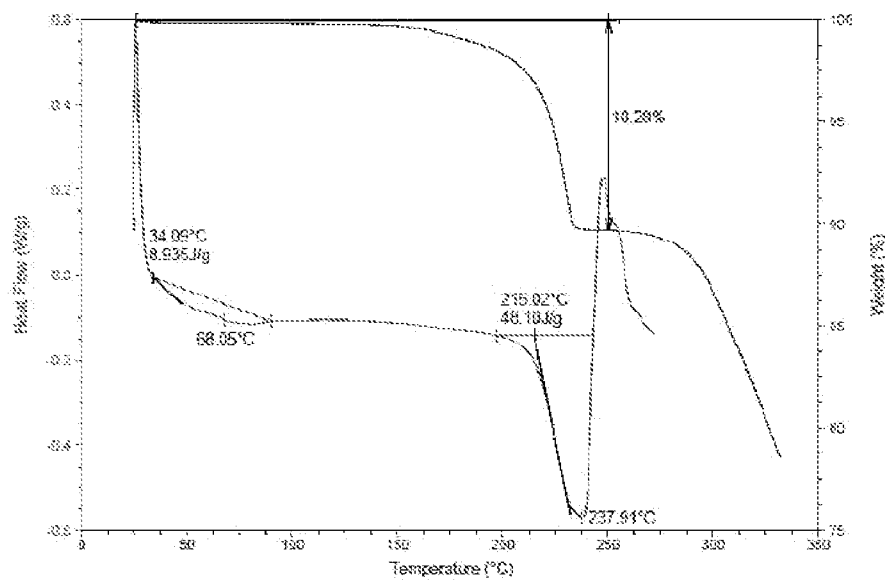


Fig. 17A

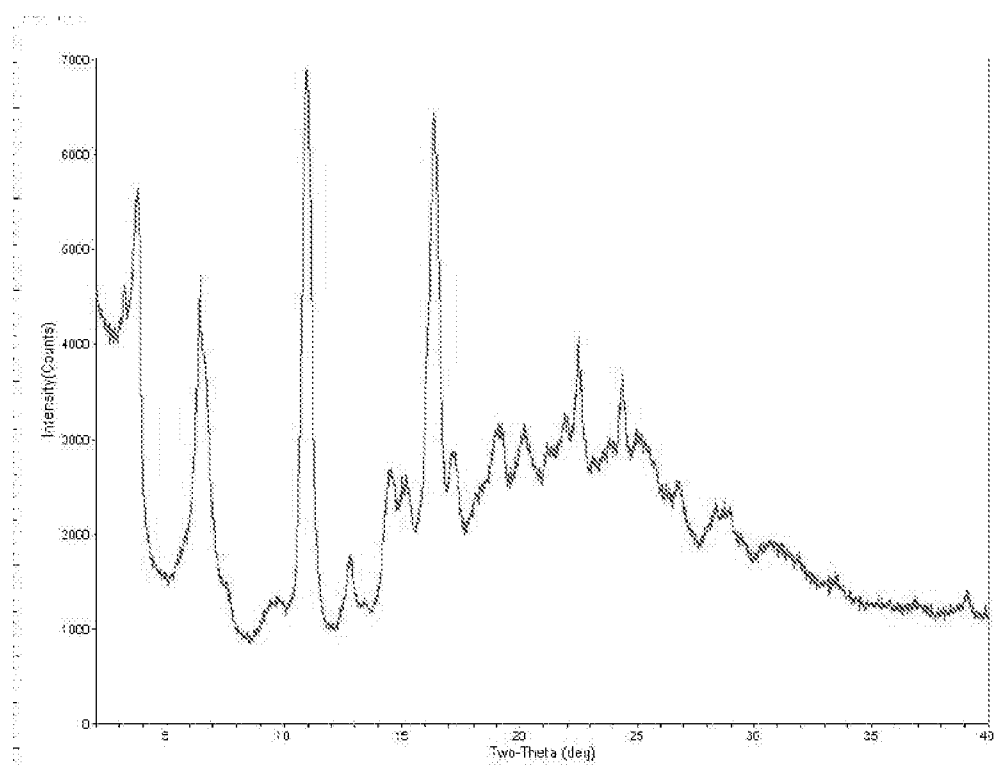


Fig. 17B

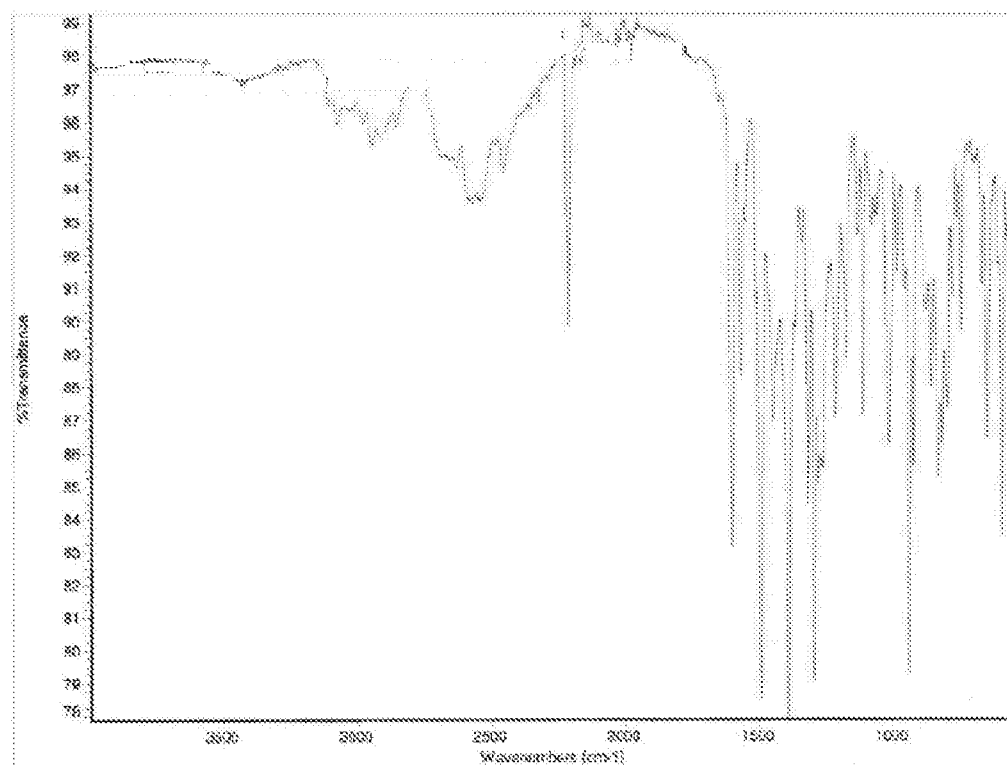


Fig. 17C

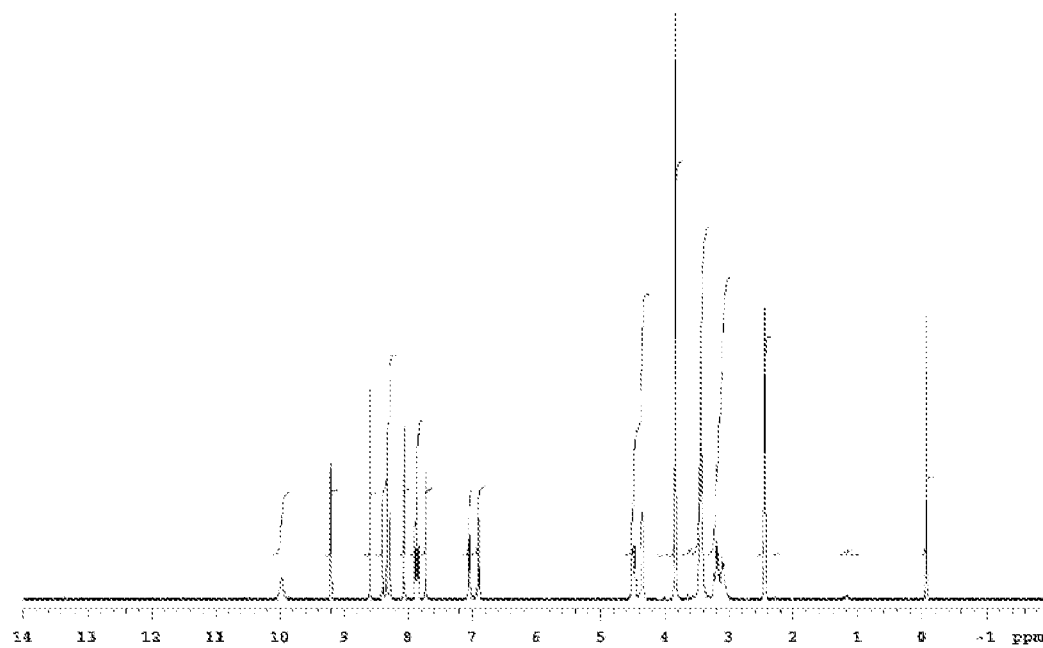


Fig. 17D

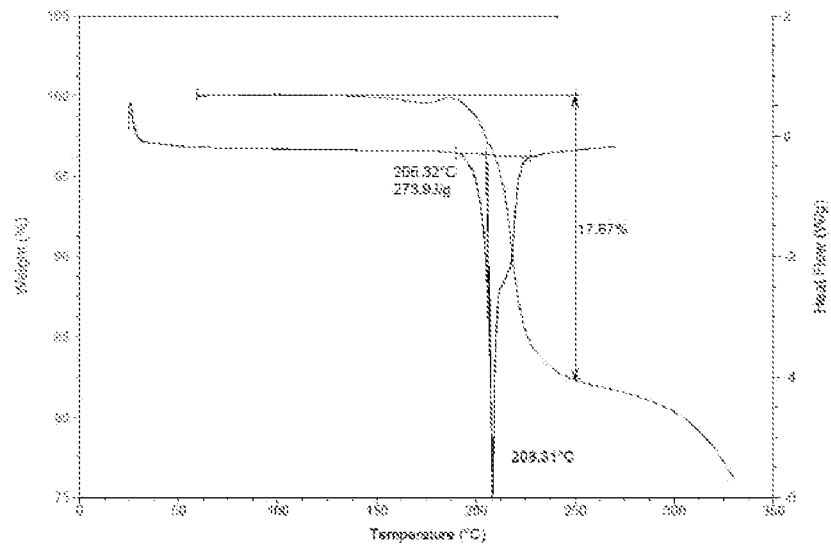


Fig. 18A

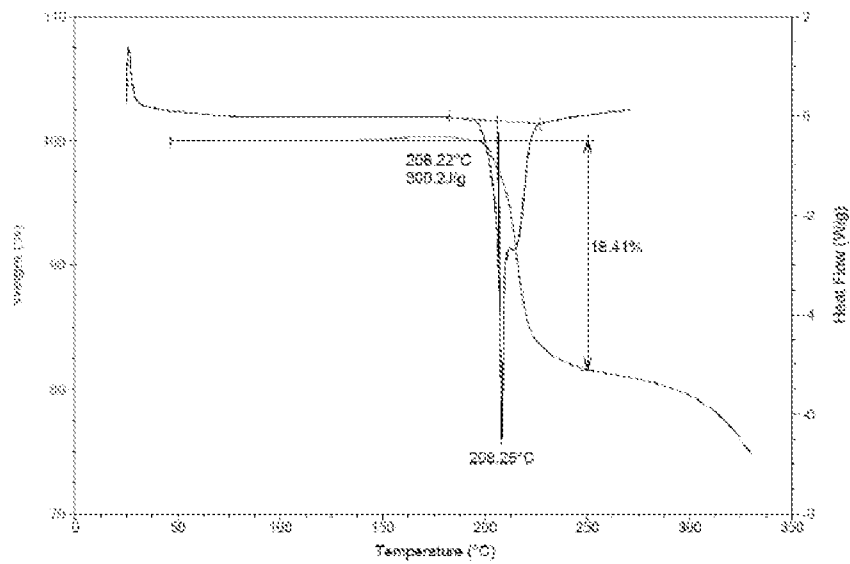


Fig. 18B

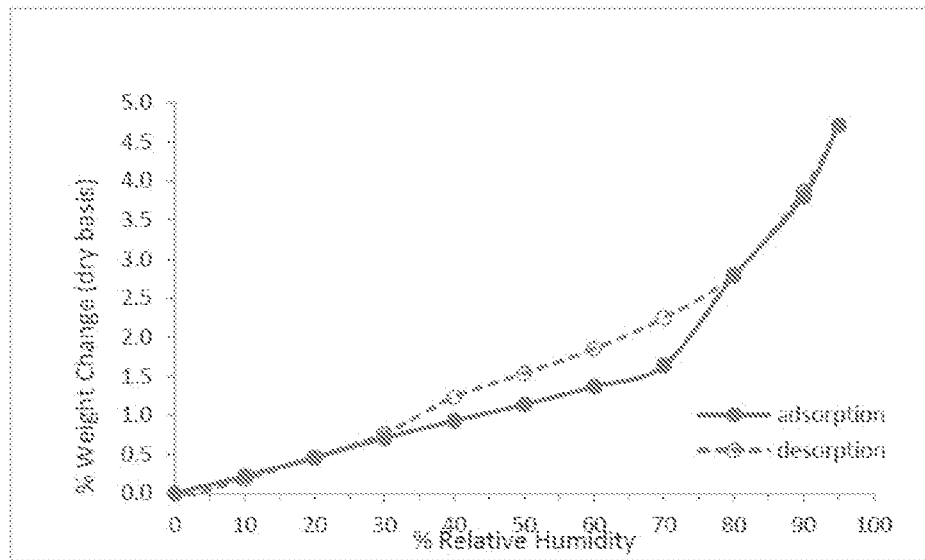


Fig. 18C

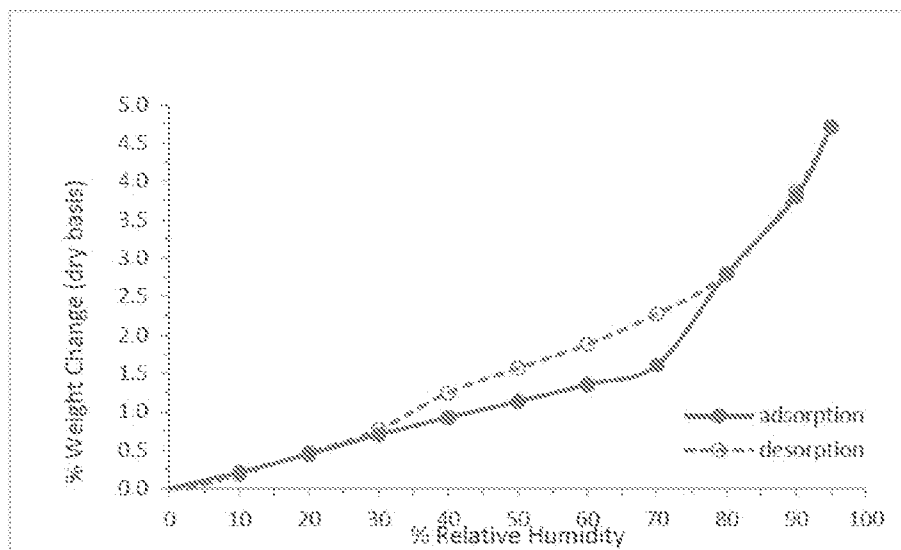


Fig. 18D

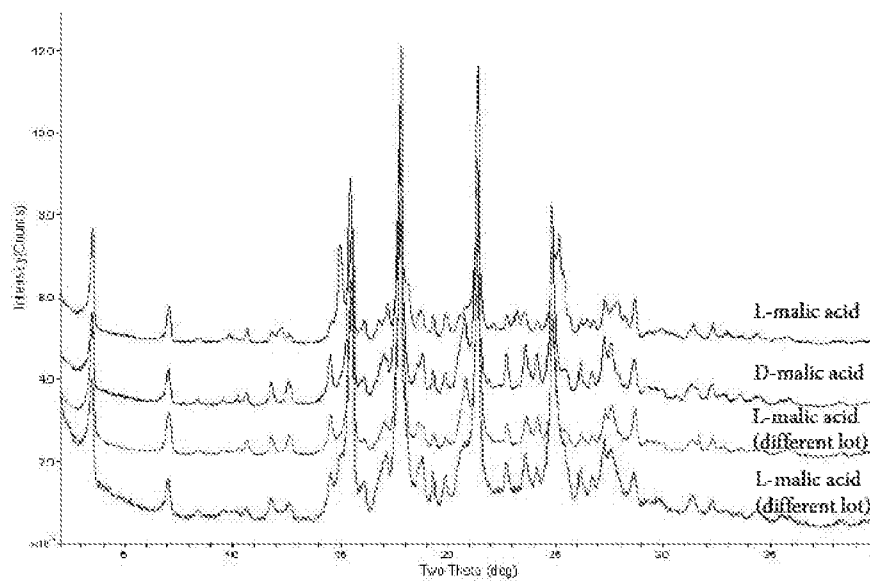


Fig. 18E

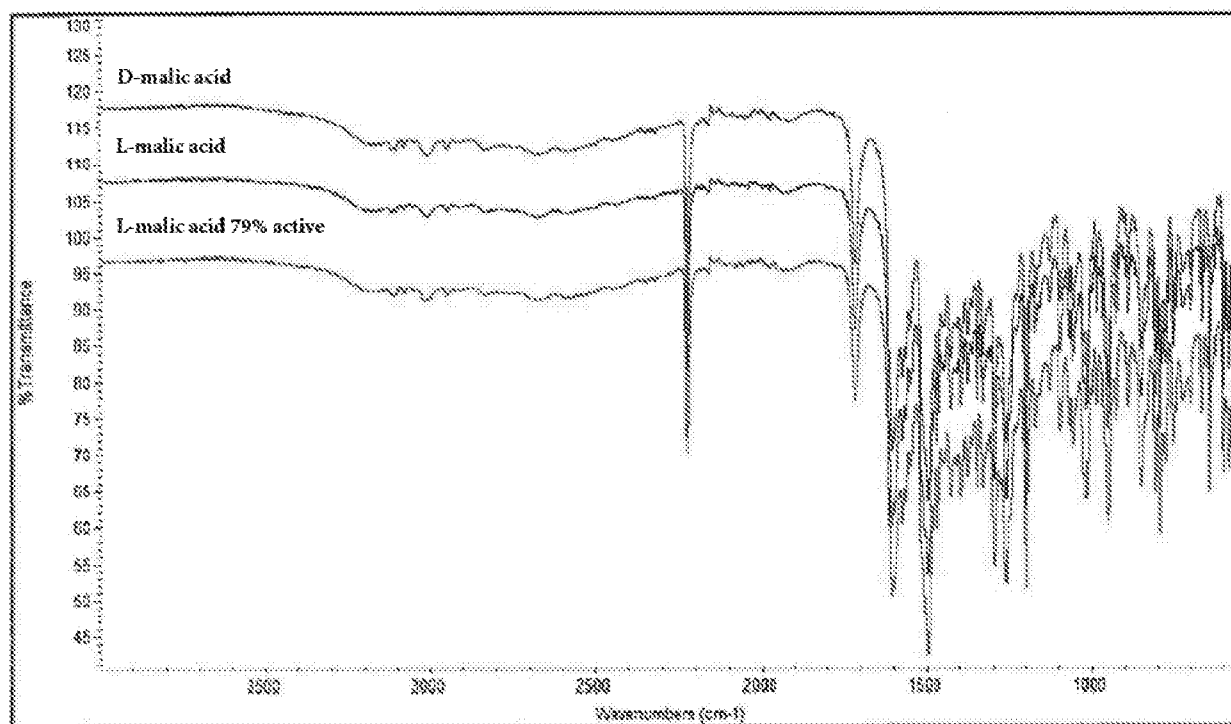


Fig. 18F

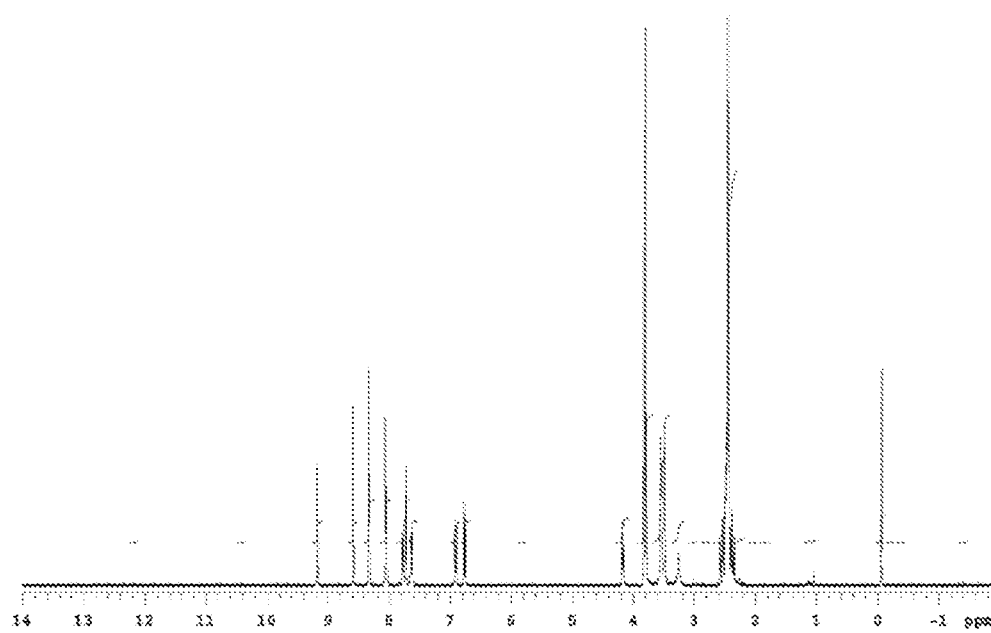


Fig. 18G

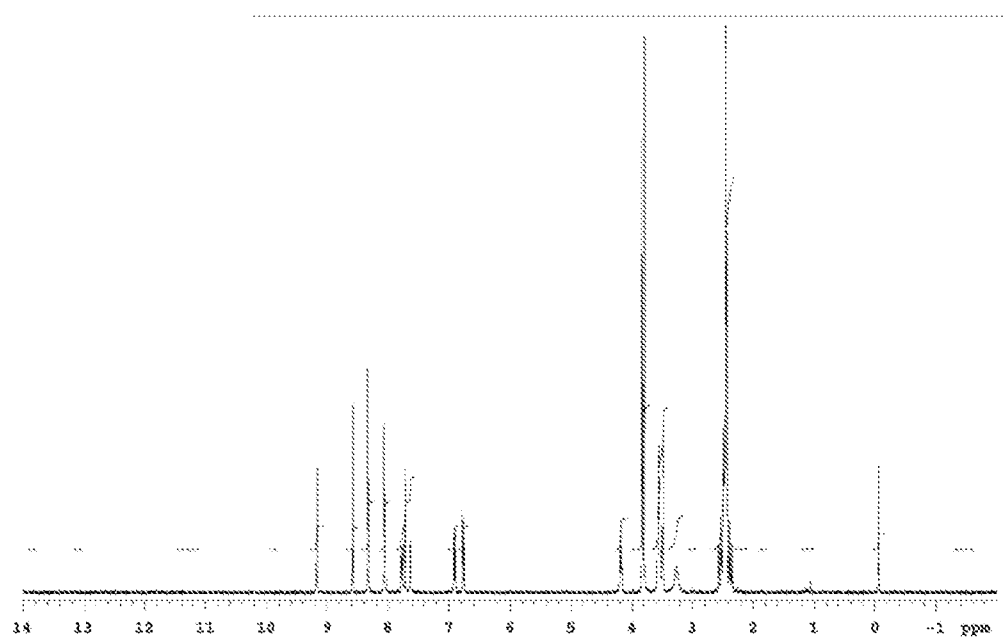


Fig. 18H

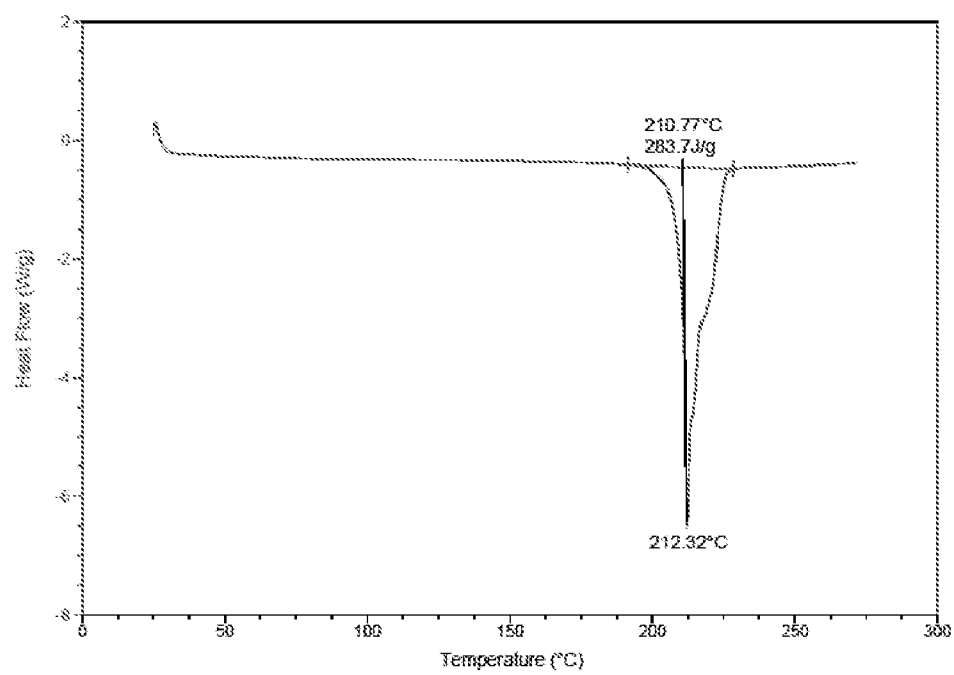


Fig. 18I

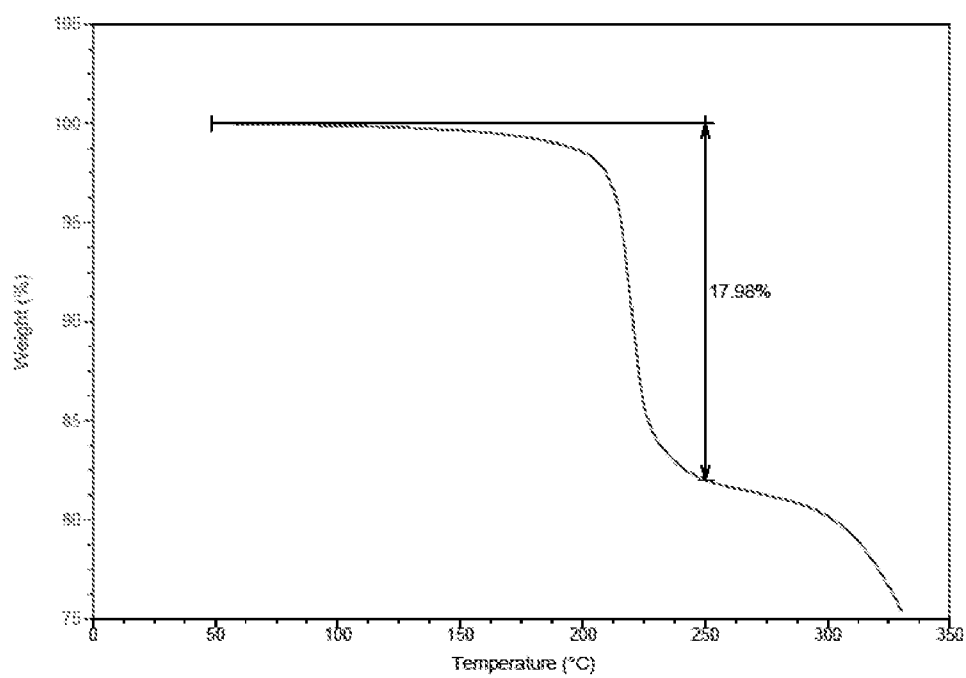


Fig. 18J

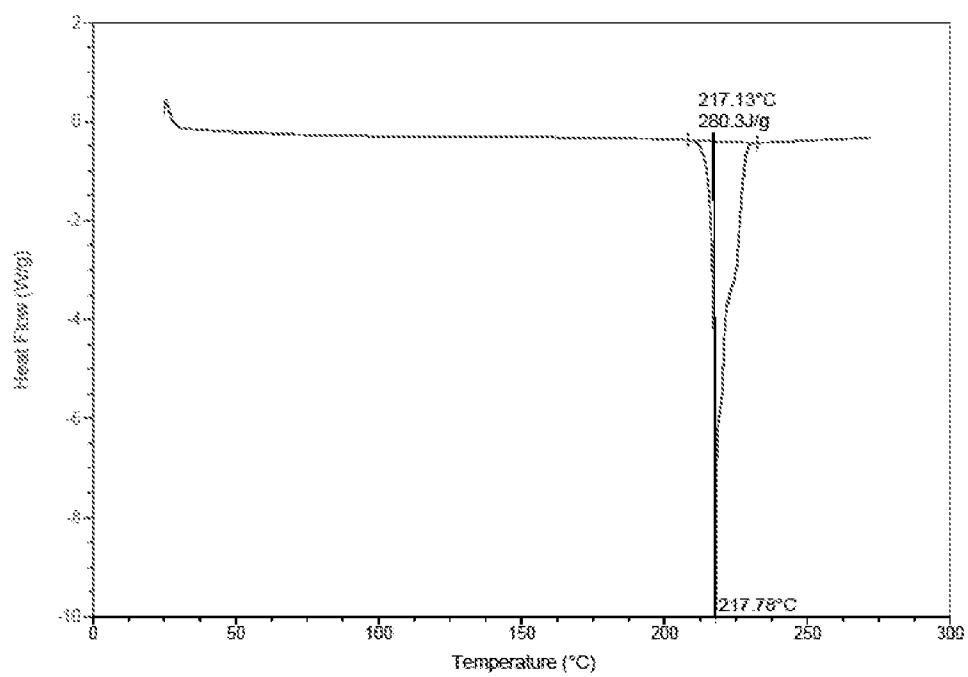


Fig. 18K

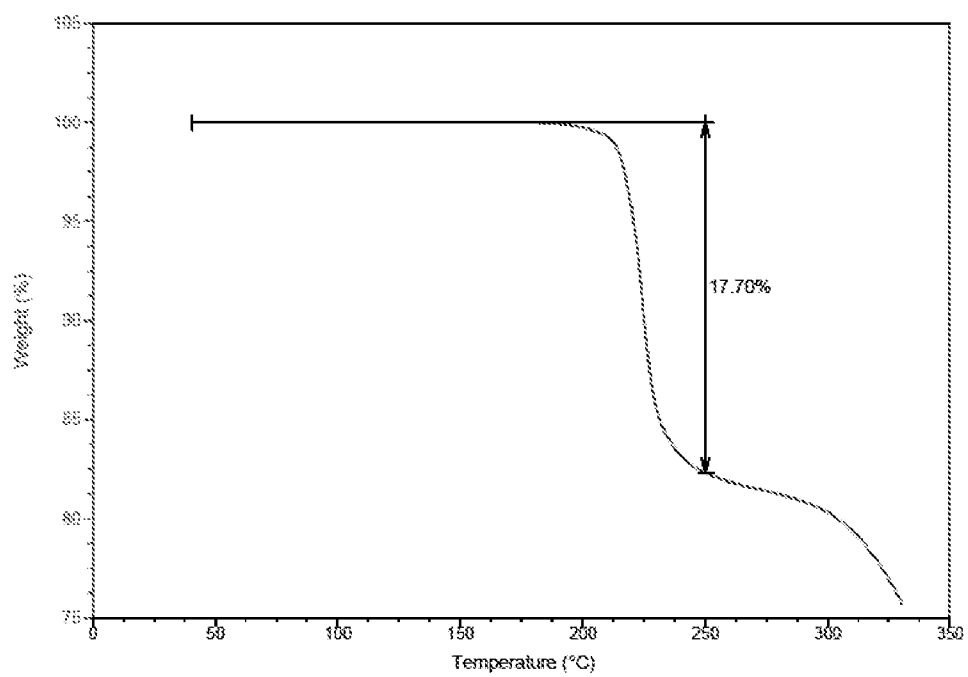


Fig. 18L

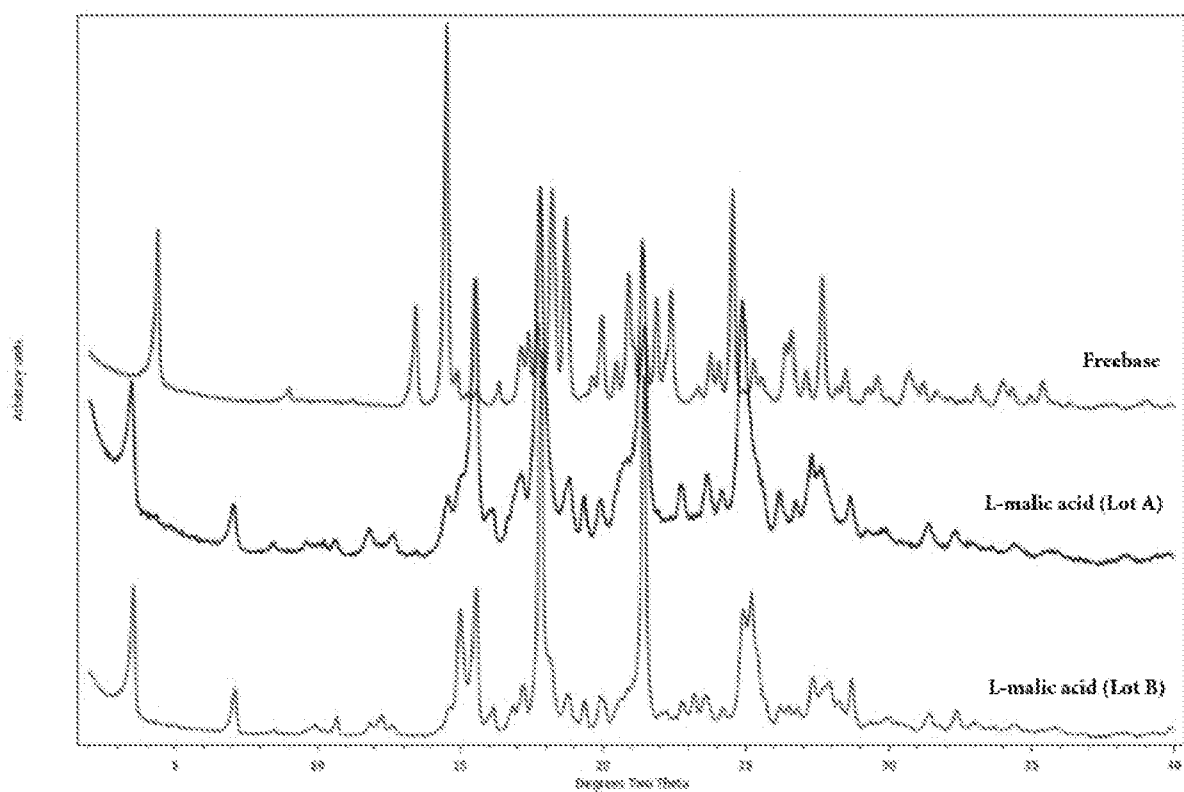


Fig. 18M

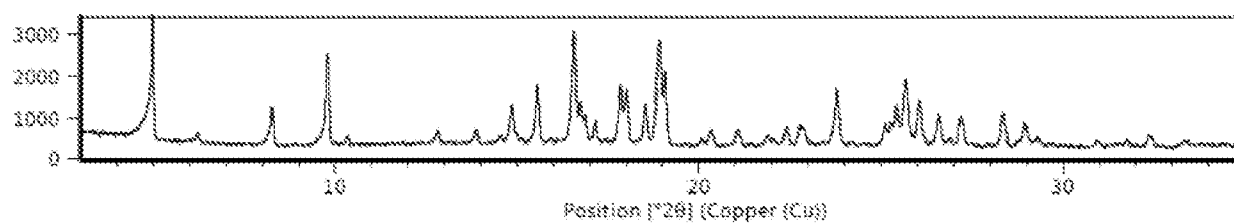


Fig. 19A

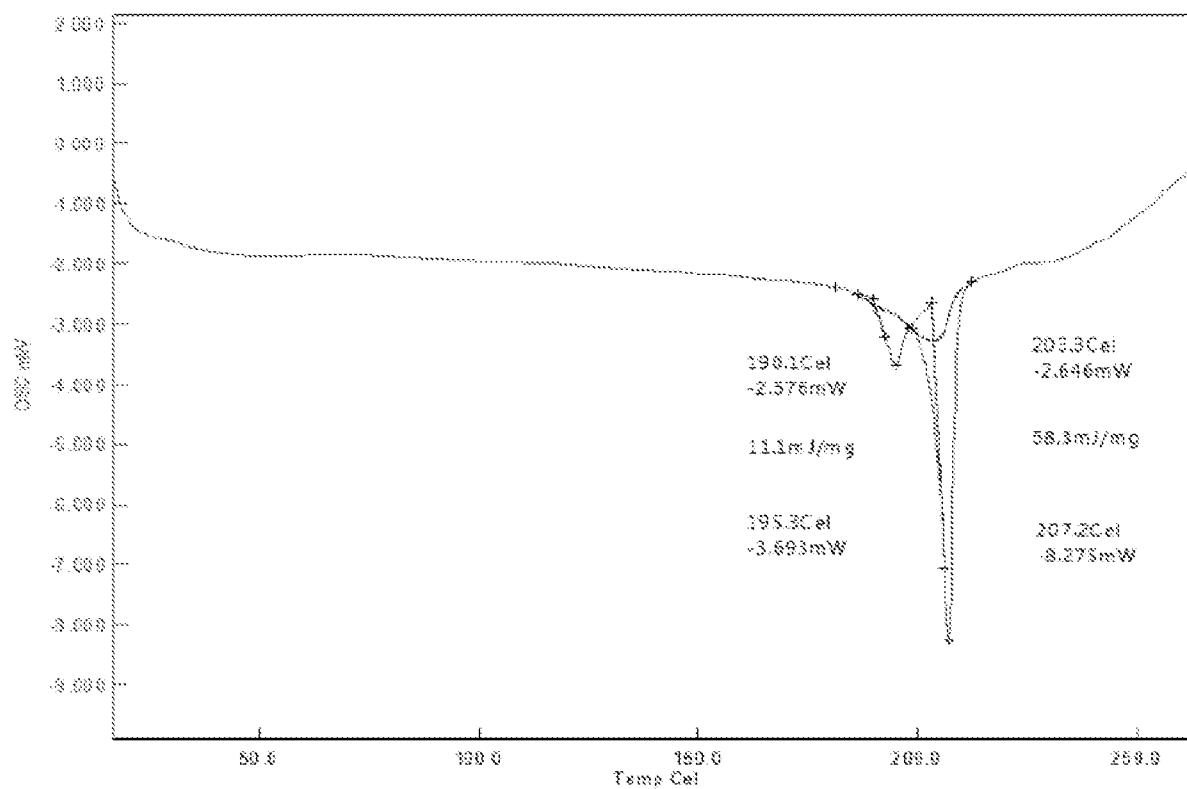


Fig. 19B

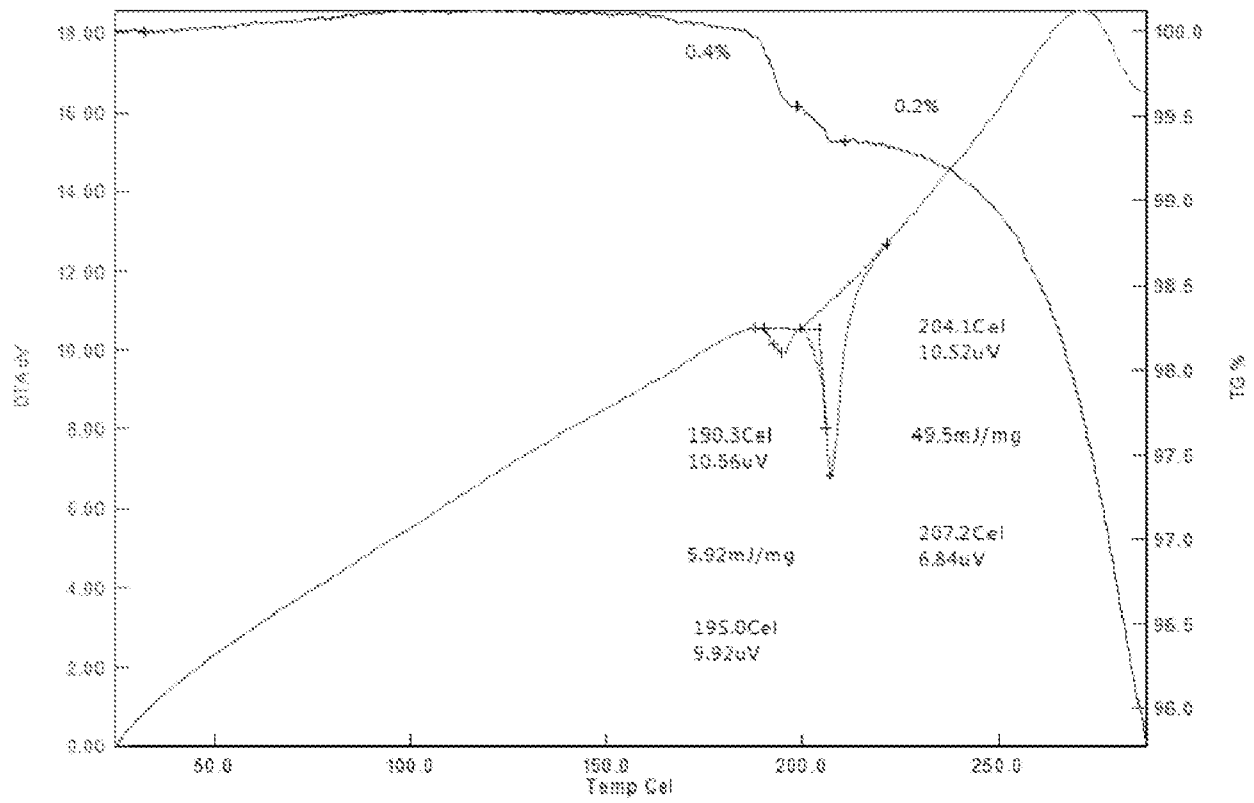


Fig. 19C

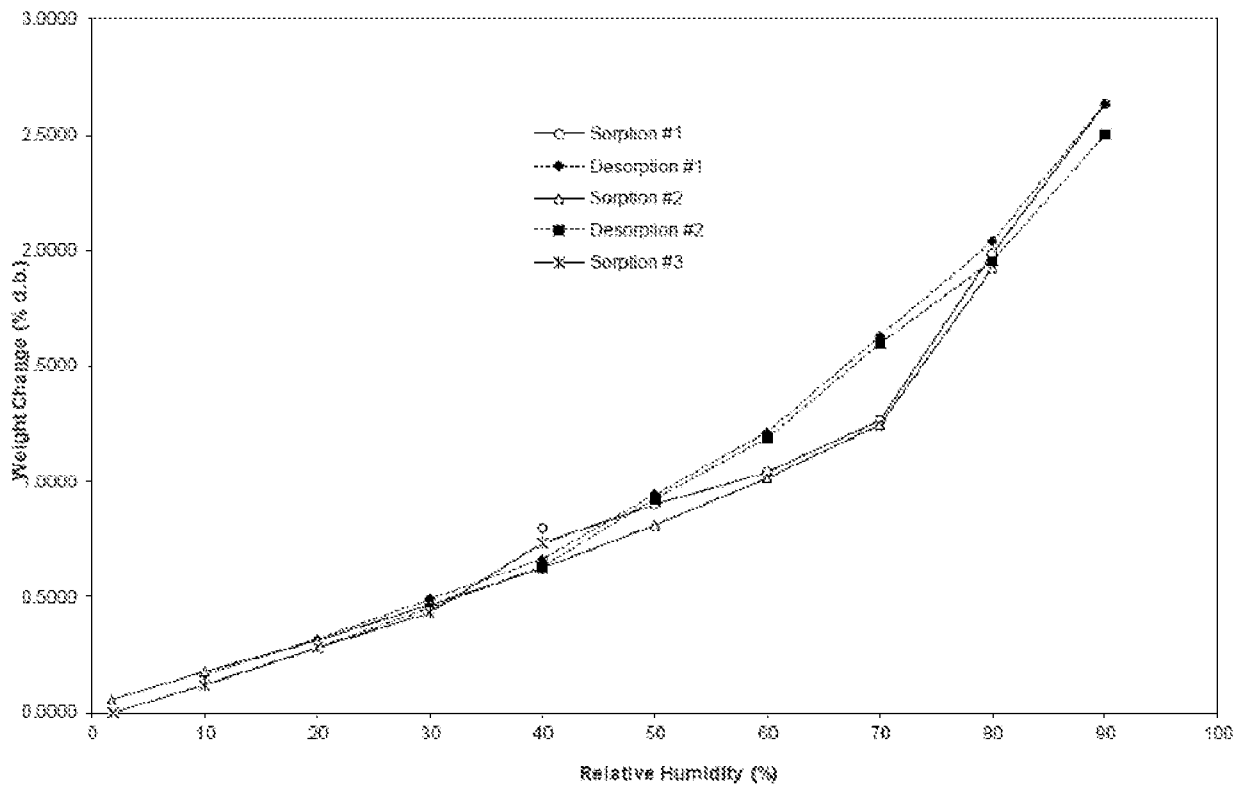


Fig. 19D

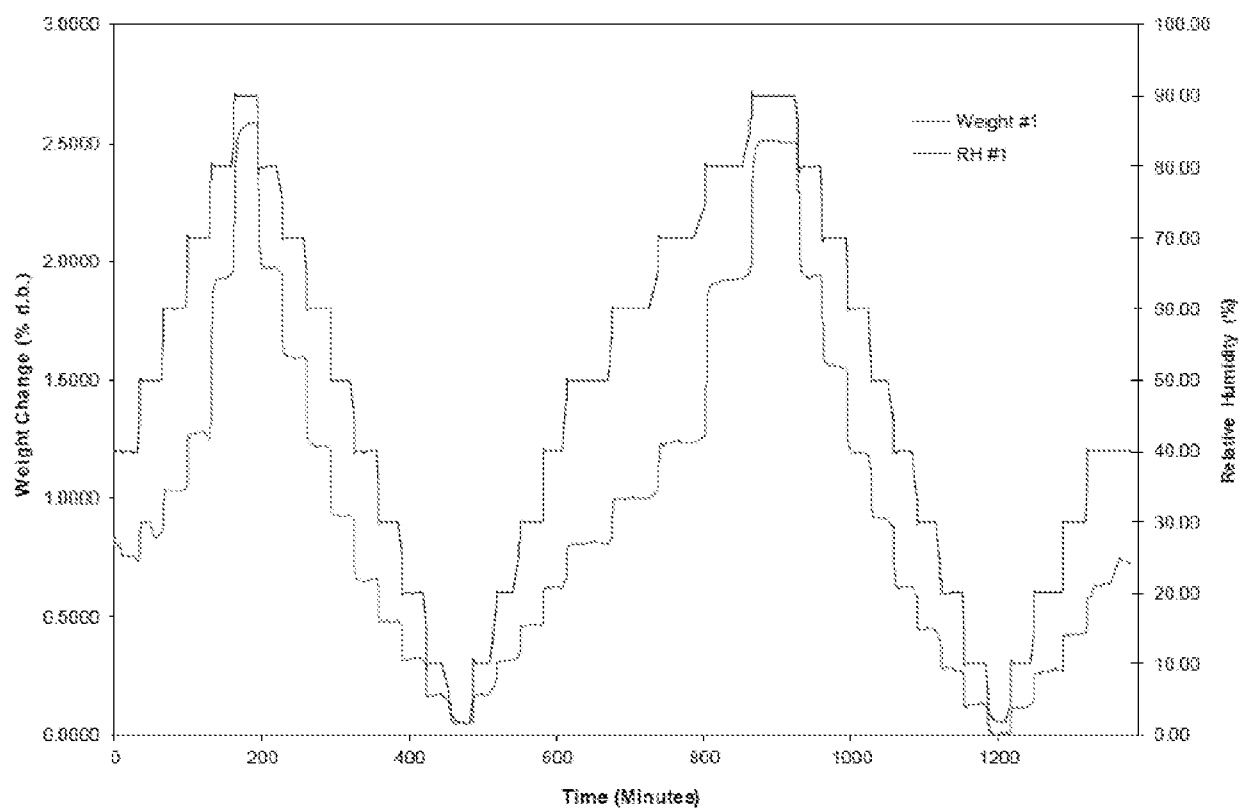


Fig. 19E

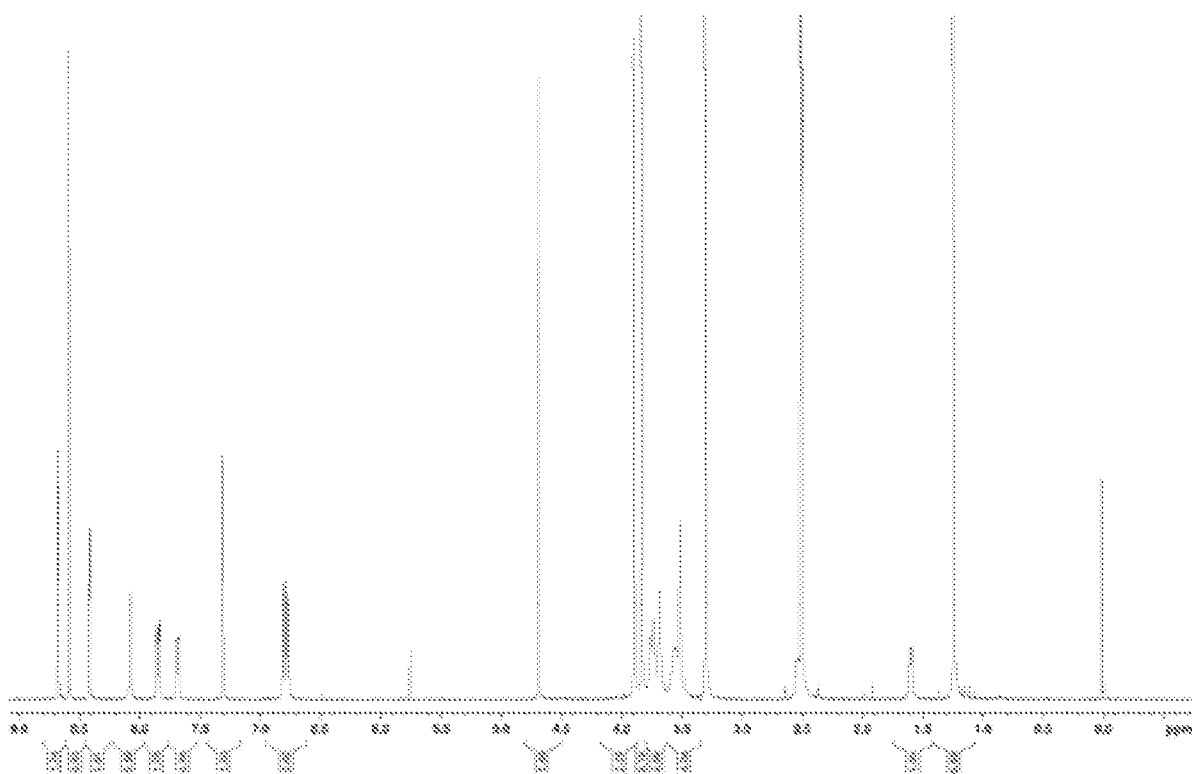


Fig. 19F

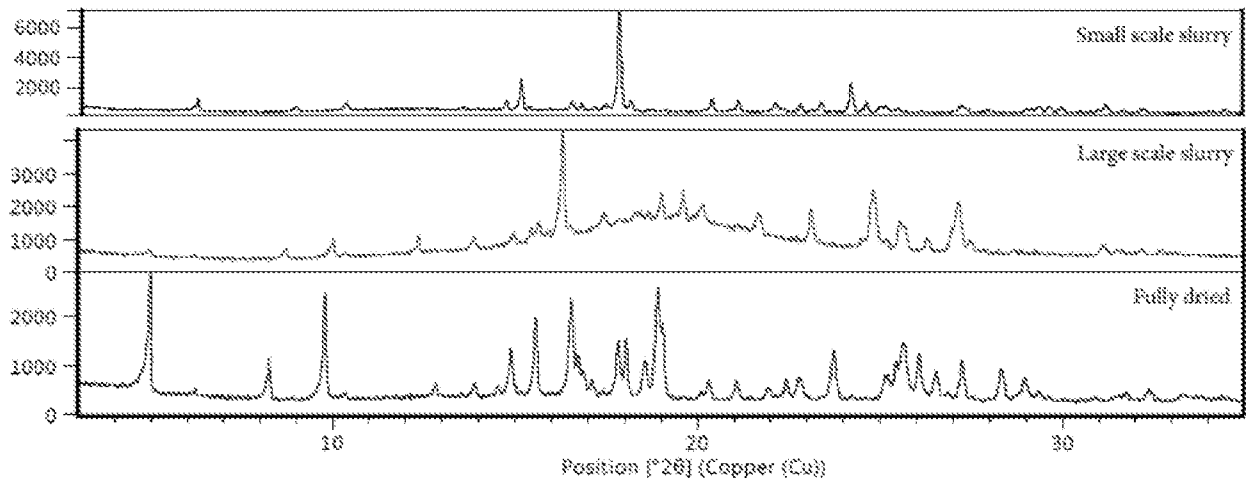


Fig. 20A

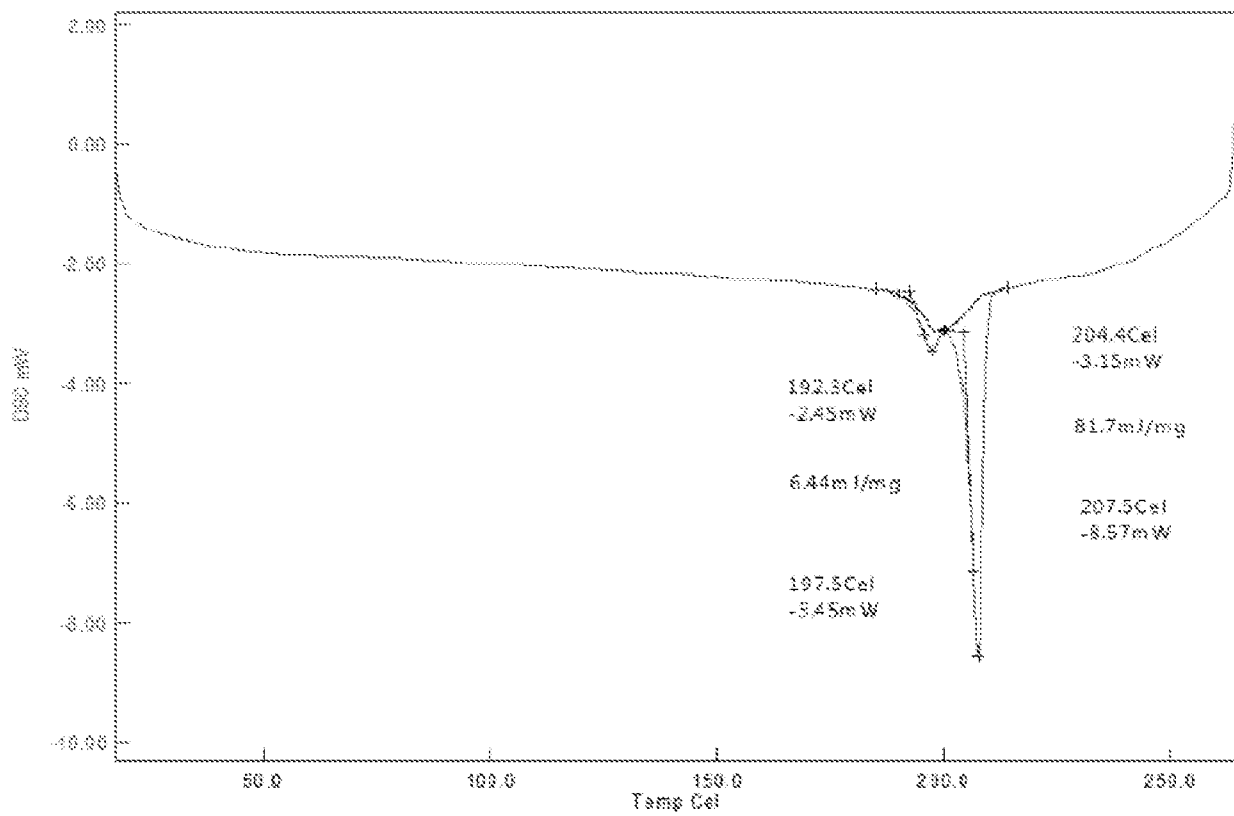


Fig. 20B

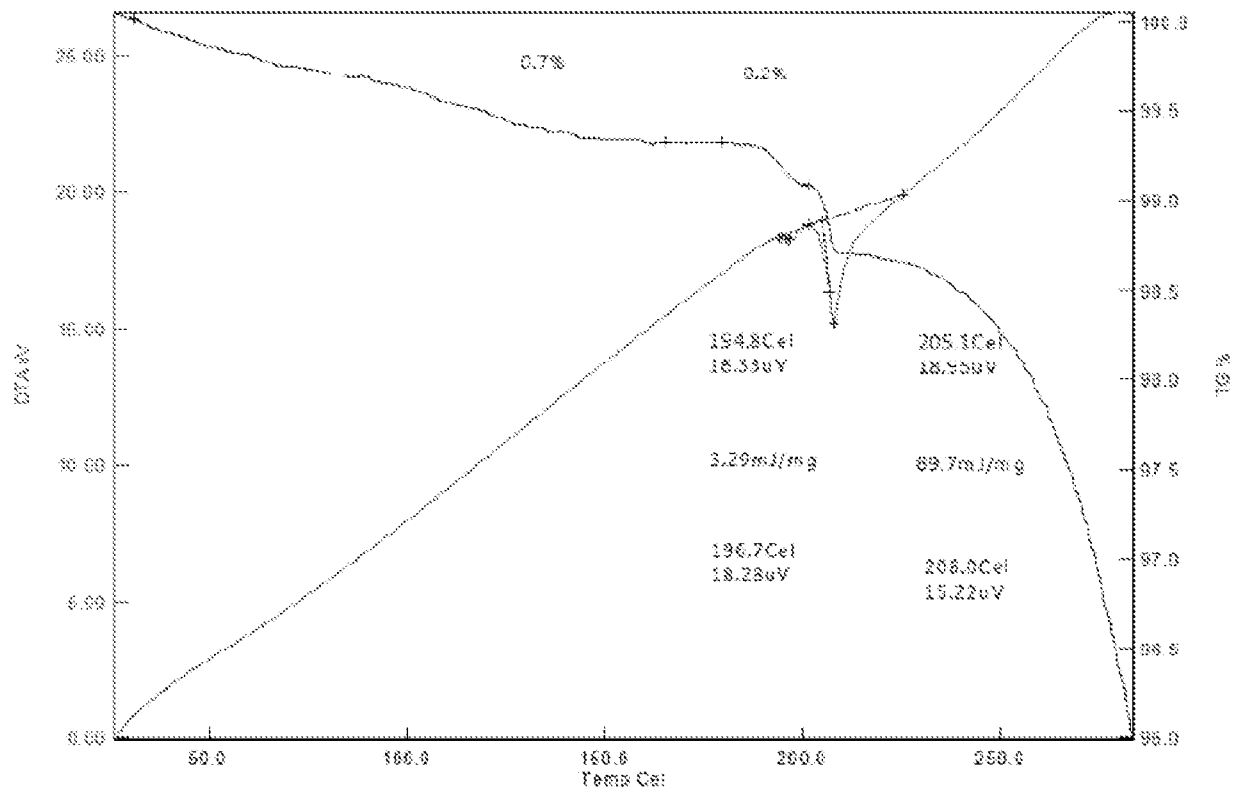


Fig. 20C

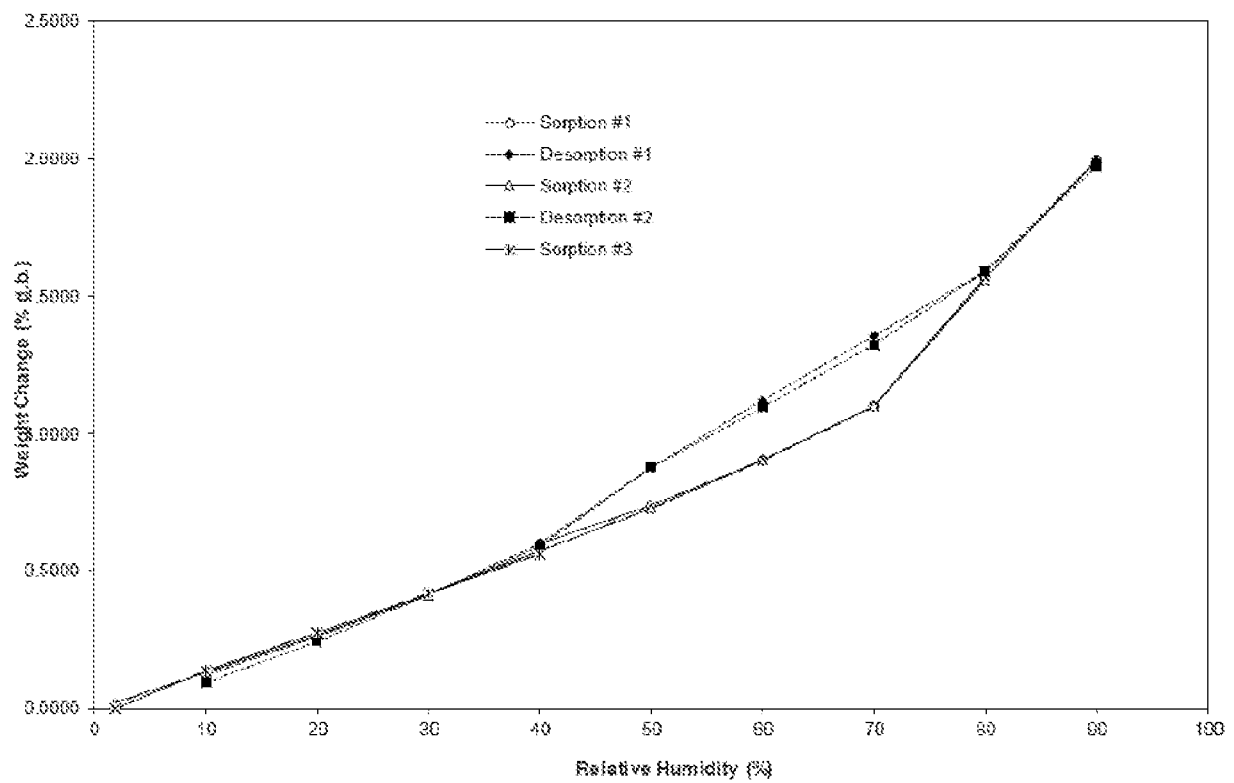


Fig. 20D

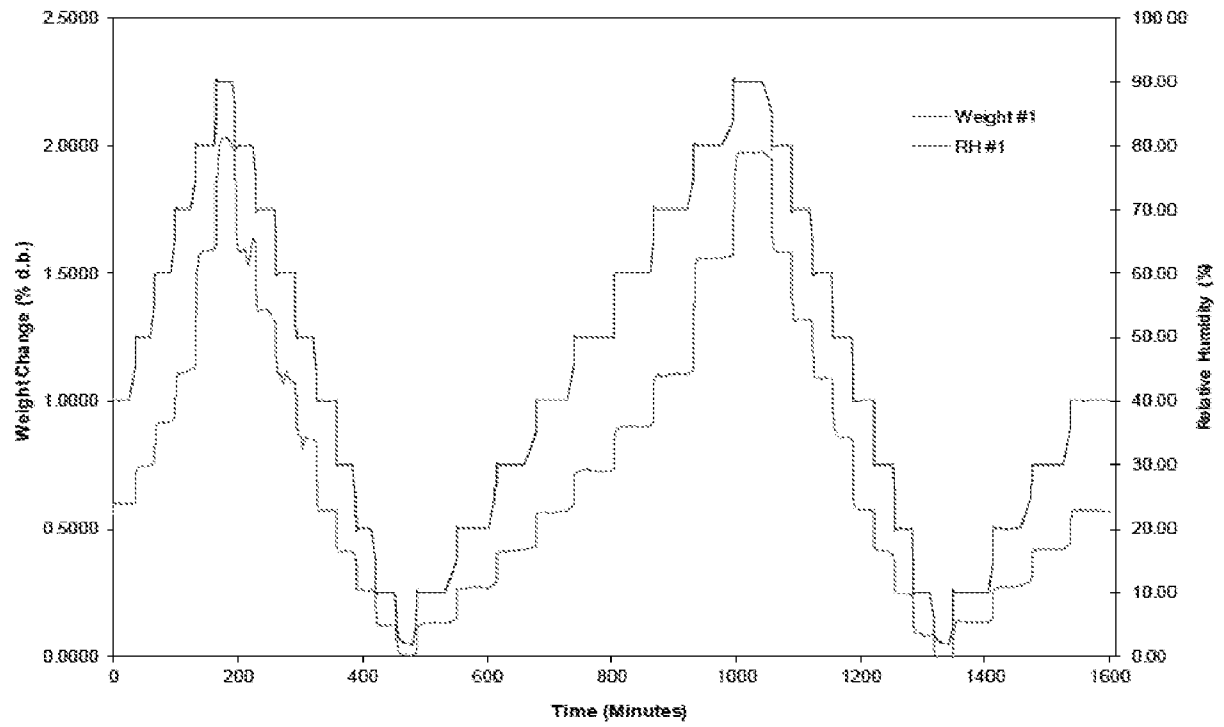


Fig. 20E

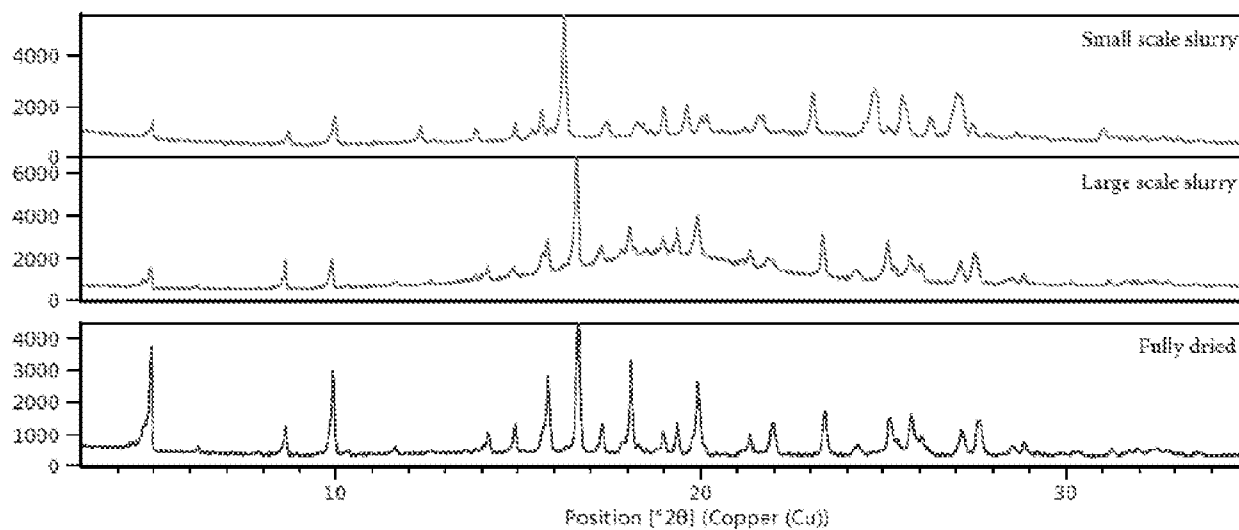


Fig. 21A

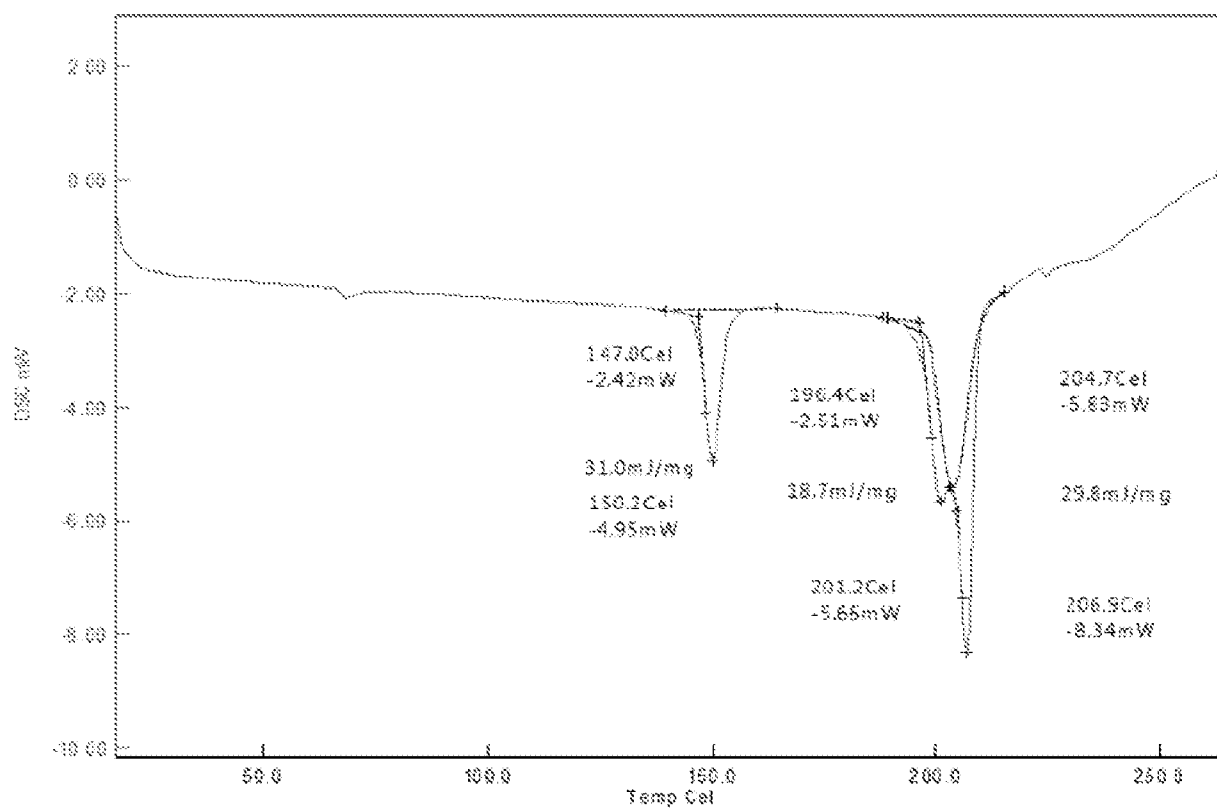


Fig. 21B

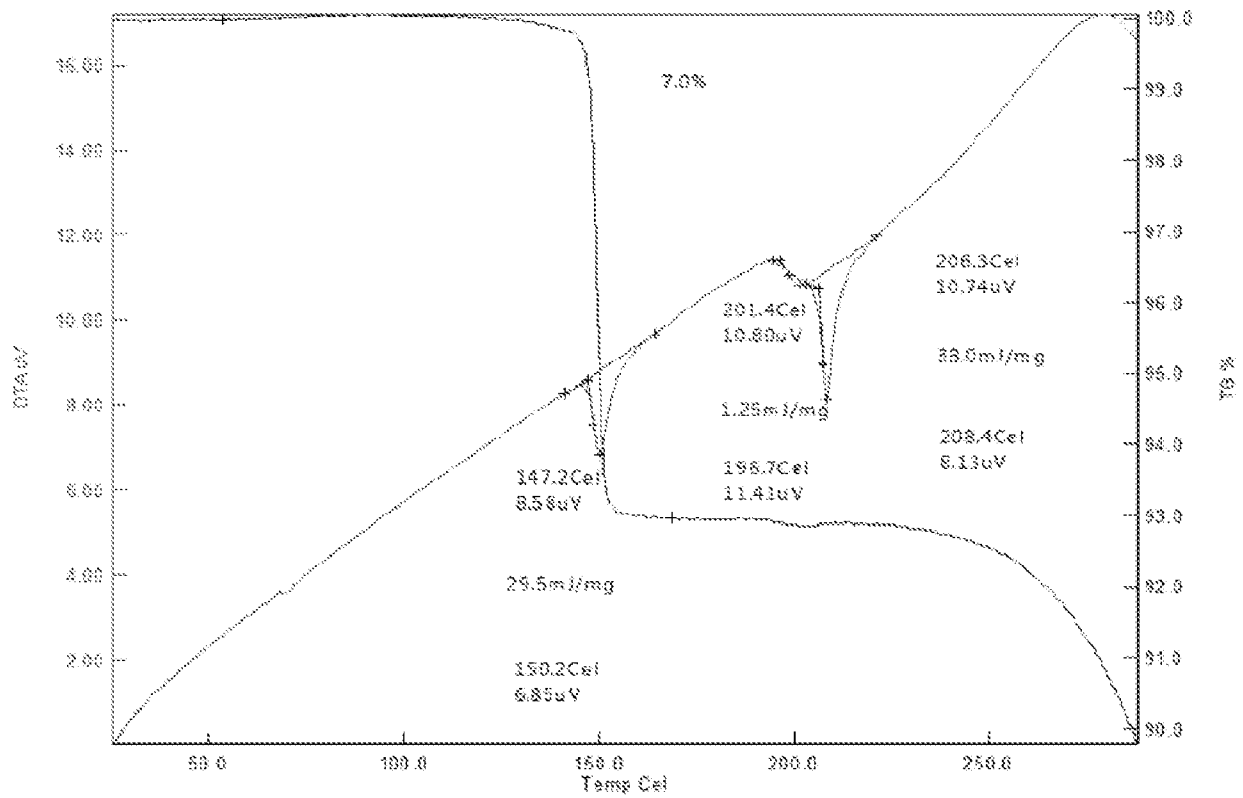


Fig. 21C

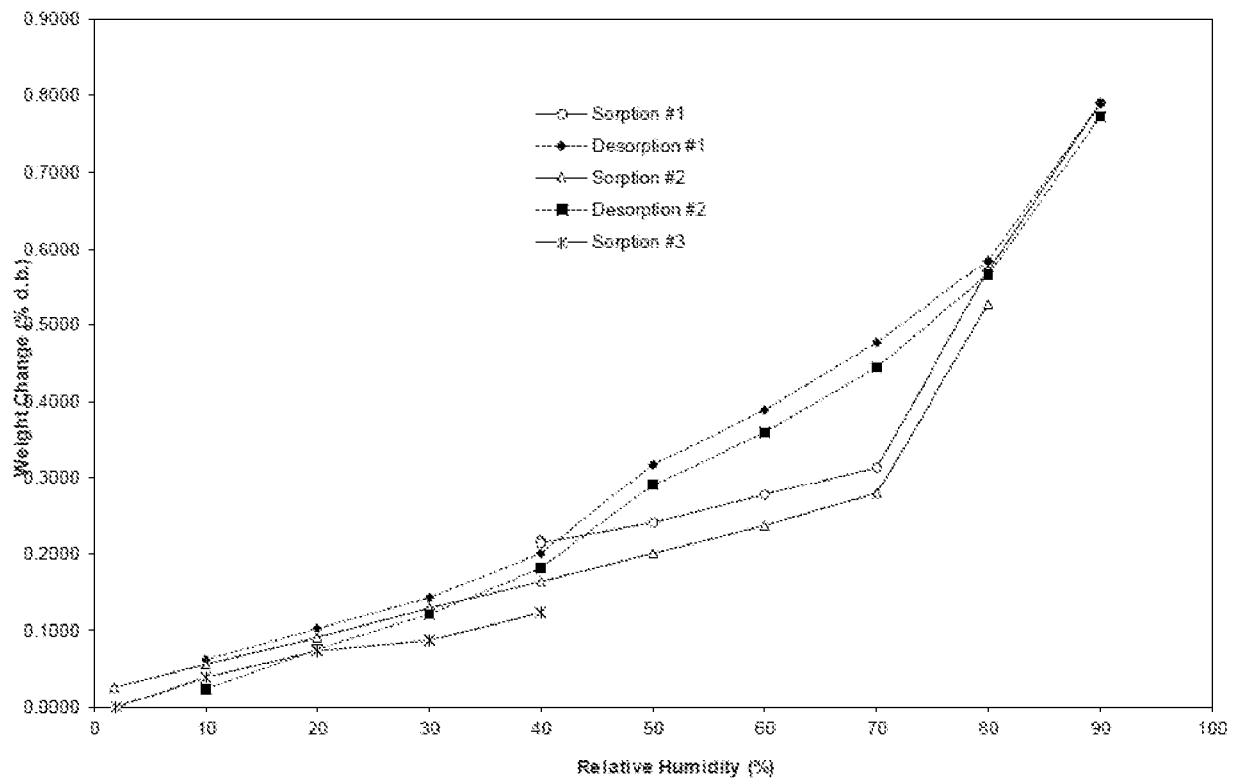


Fig. 21D

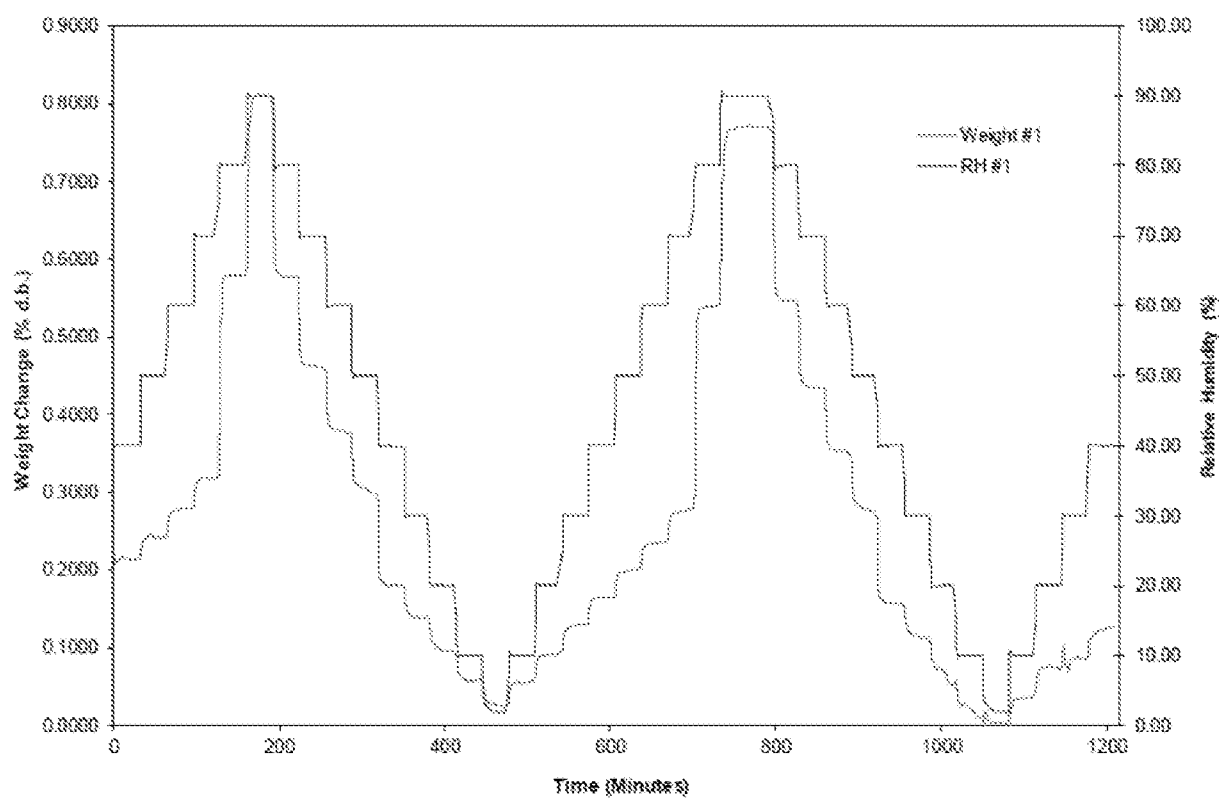


Fig. 21E

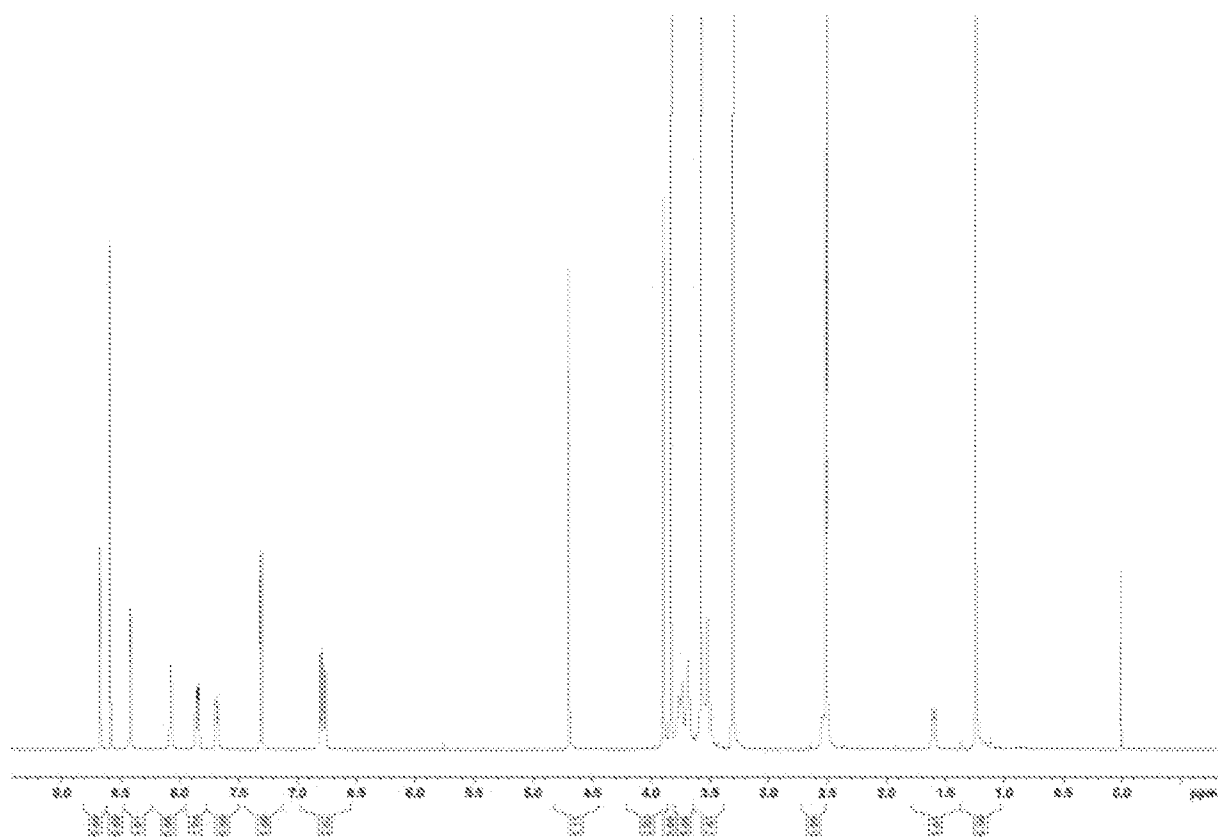


Fig. 21F

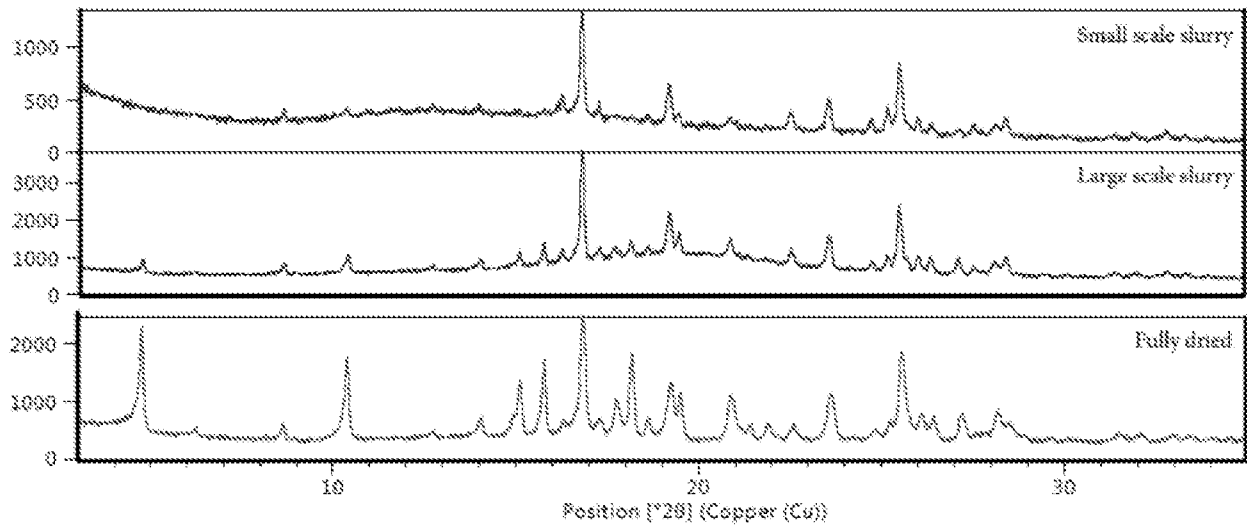


Fig. 22A

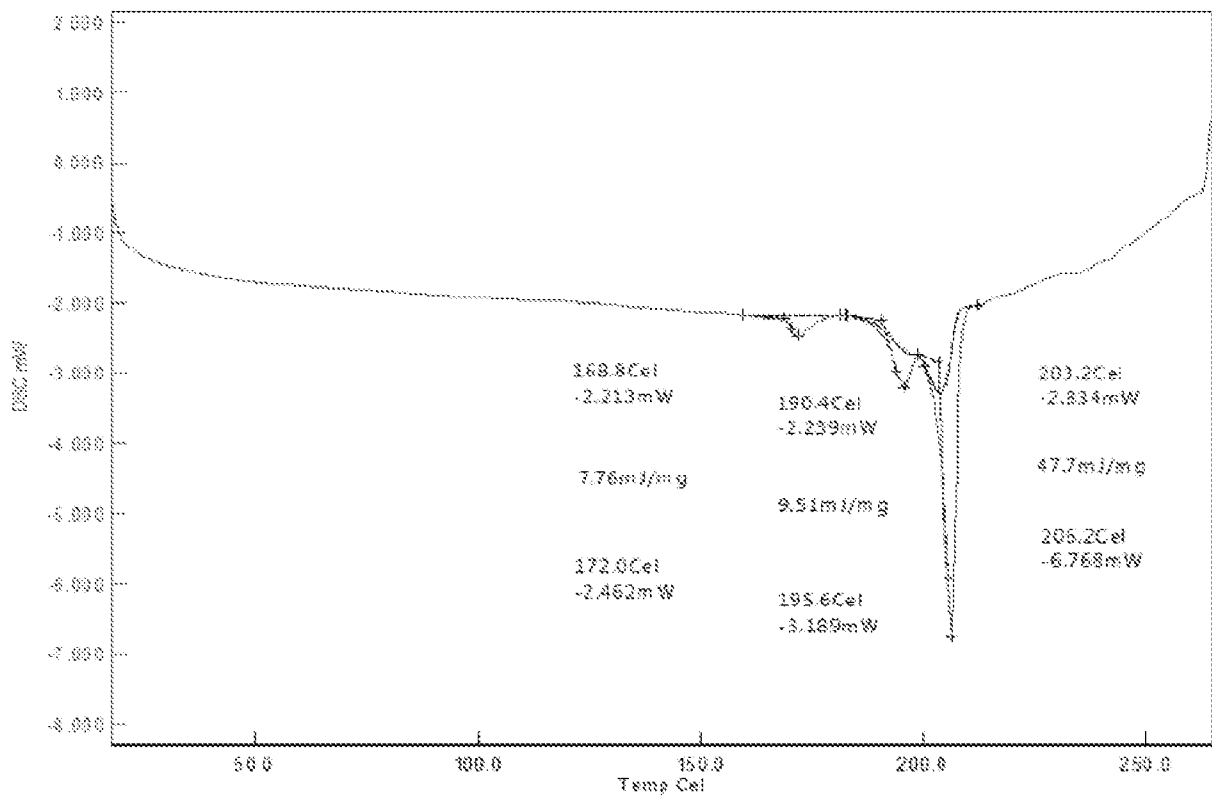


Fig. 22B

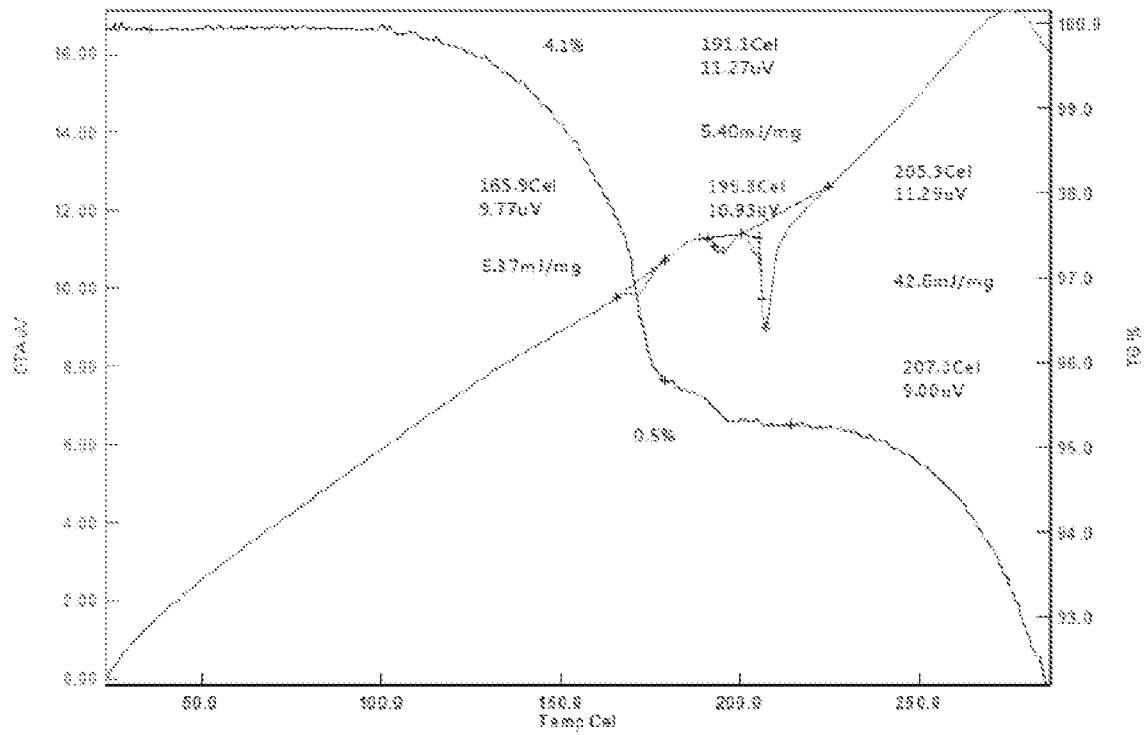


Fig. 22C

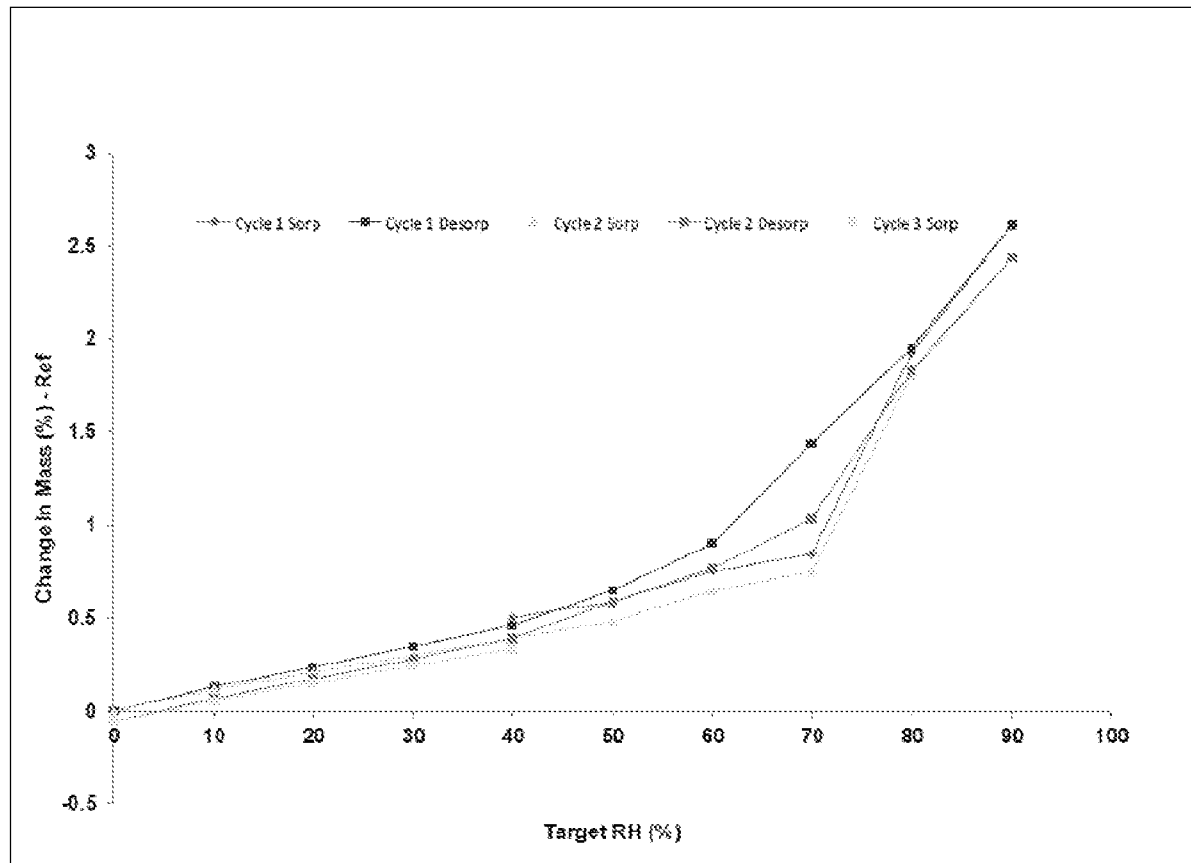


Fig. 22D

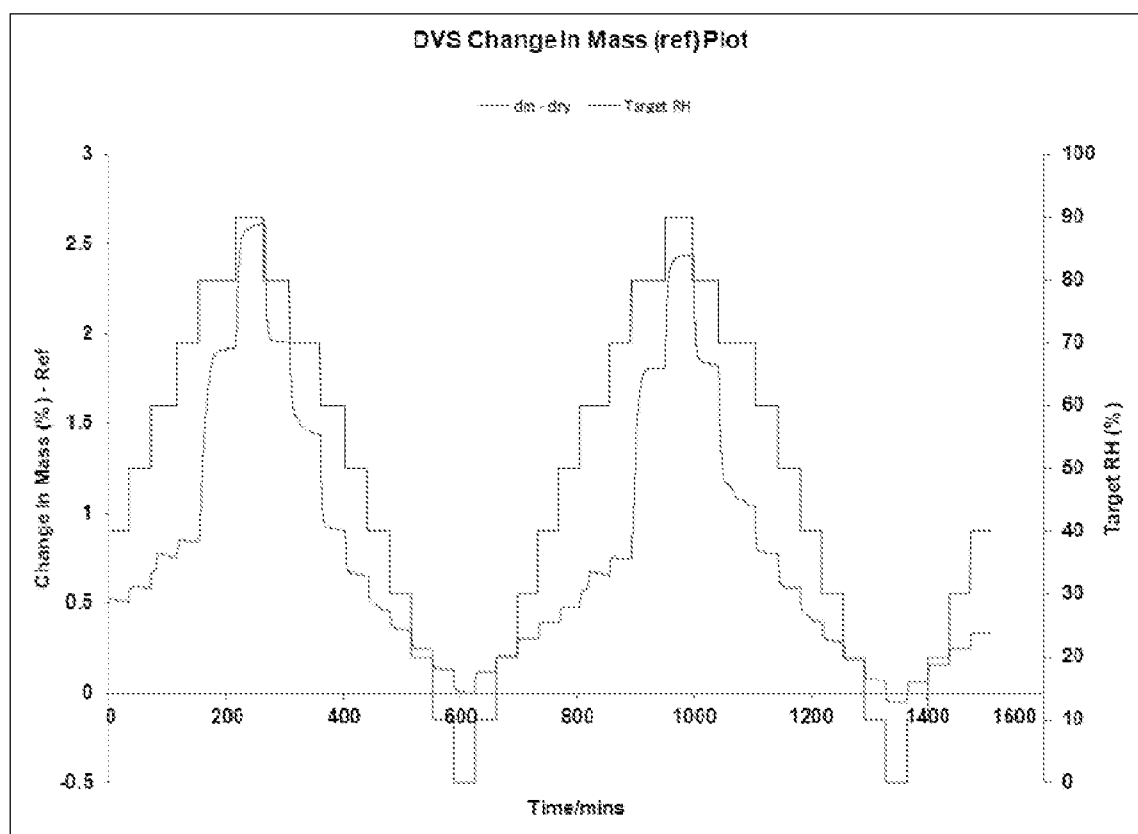


Fig. 22E

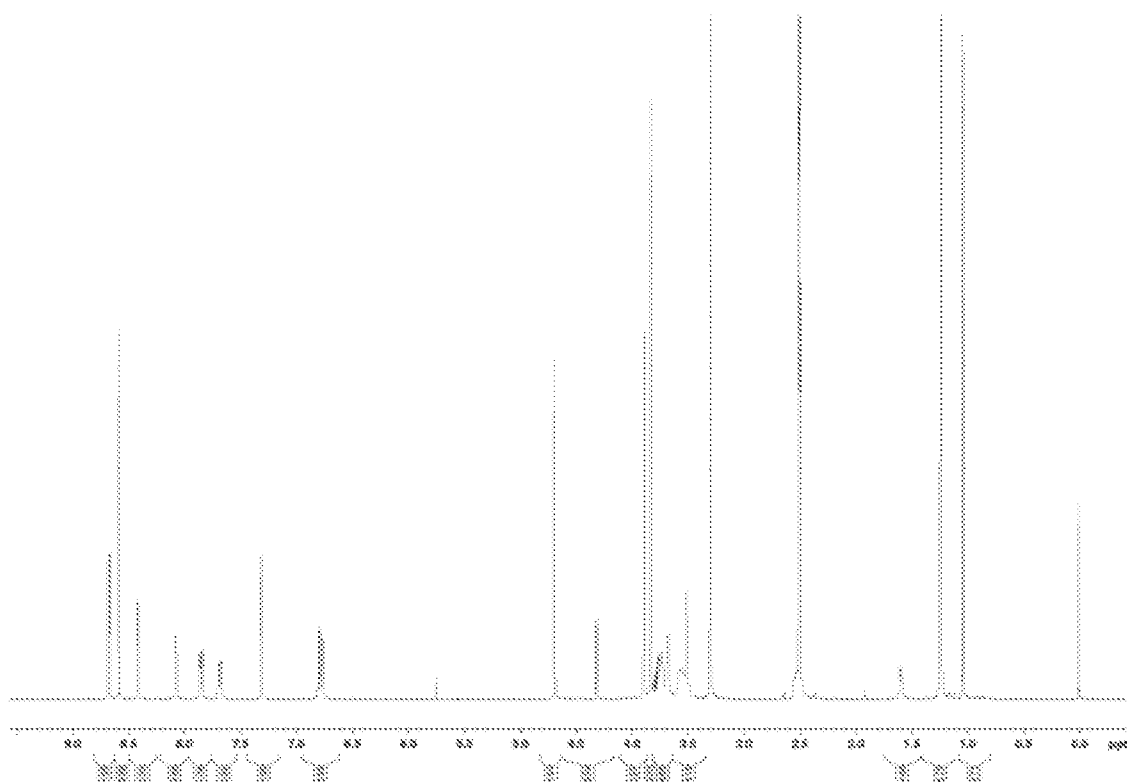


Fig. 22F

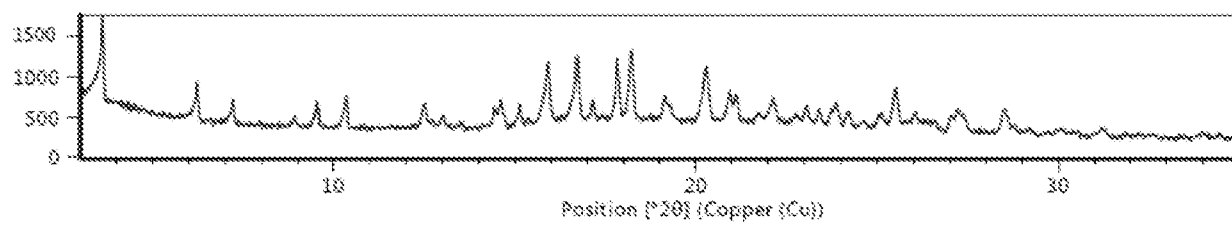


Fig. 23A

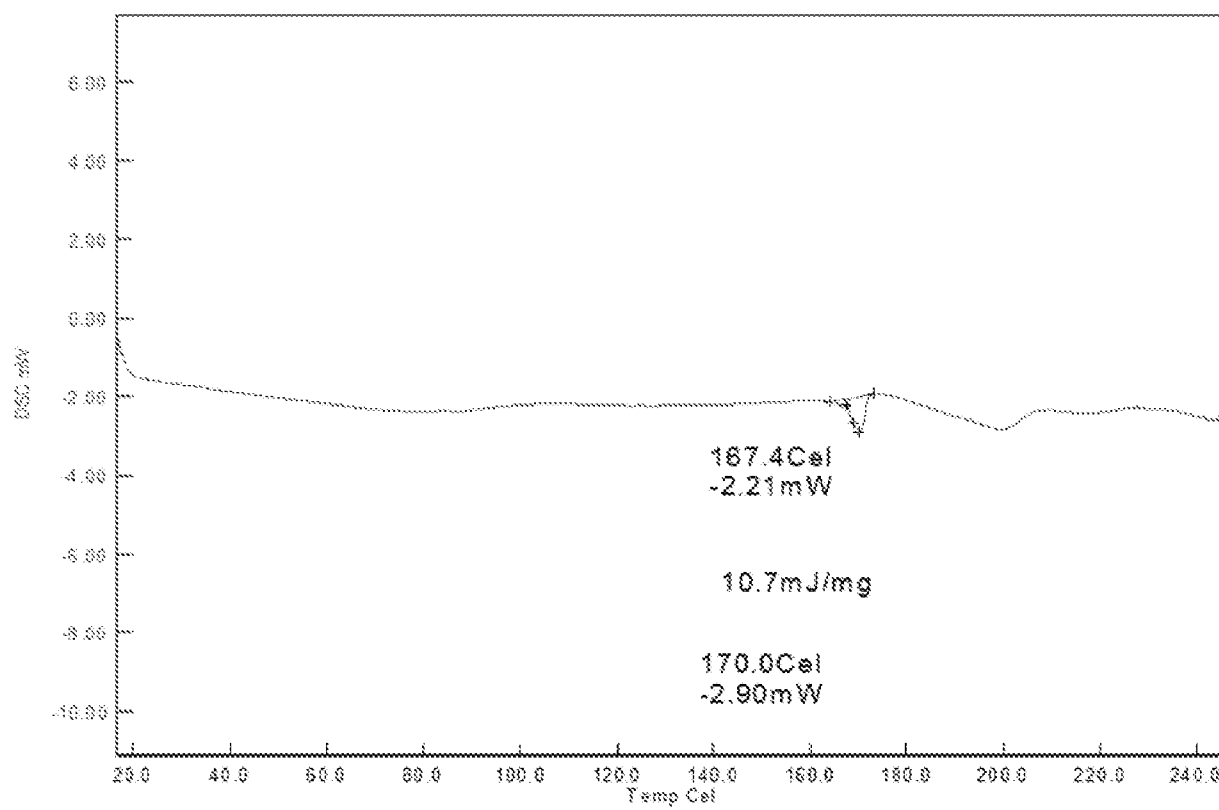


Fig. 23B

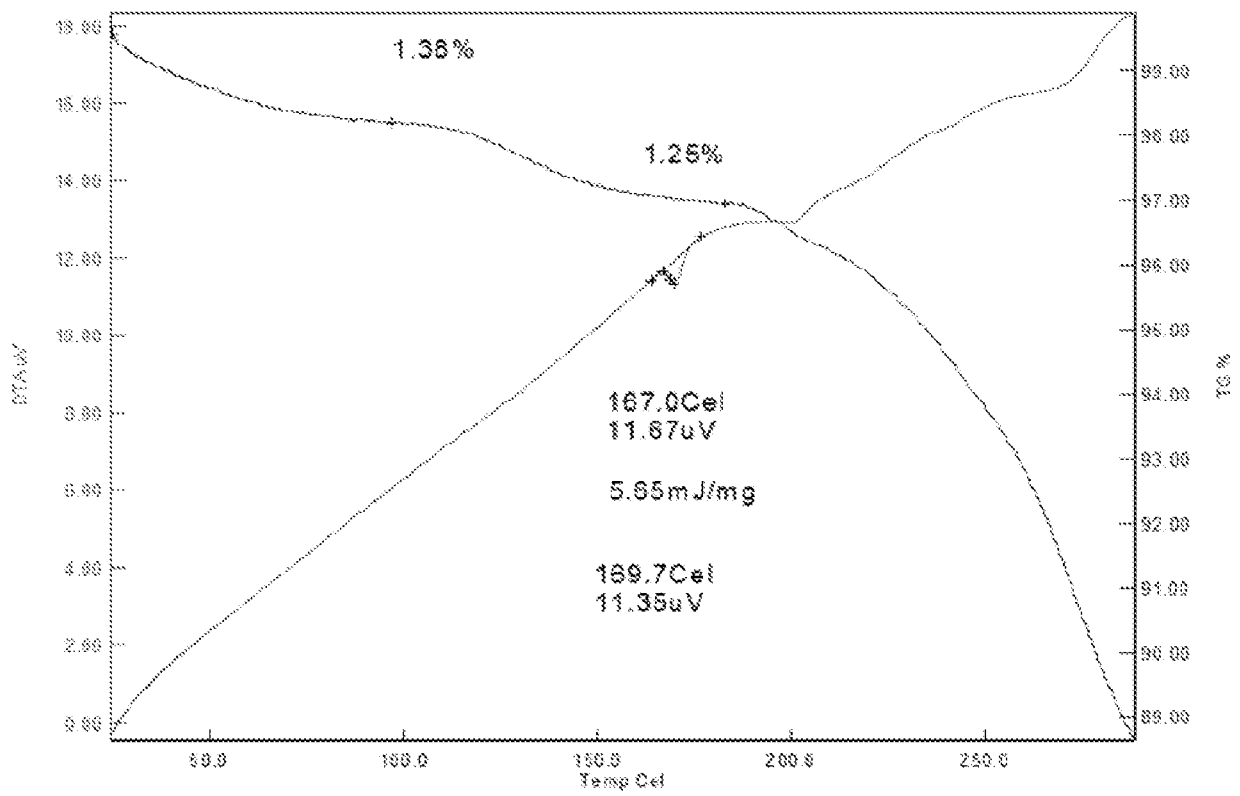


Fig. 23C

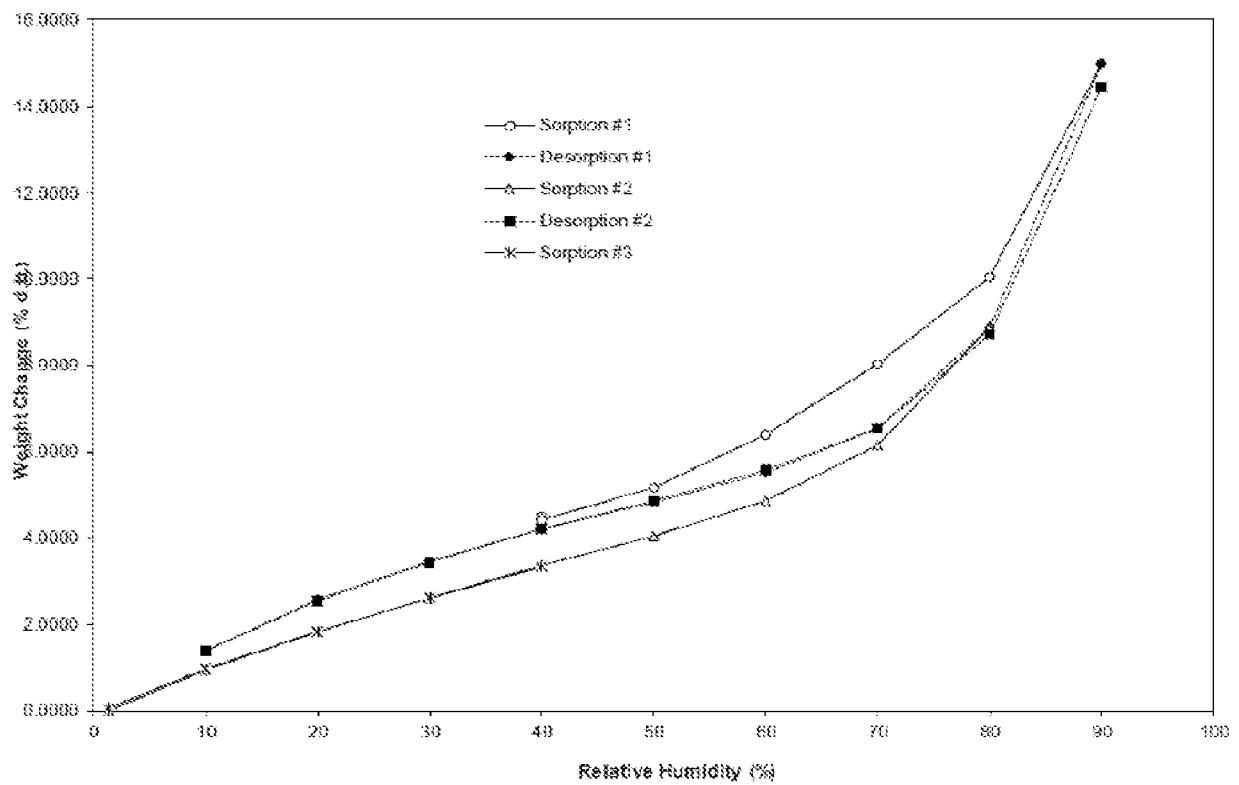


Fig. 23D

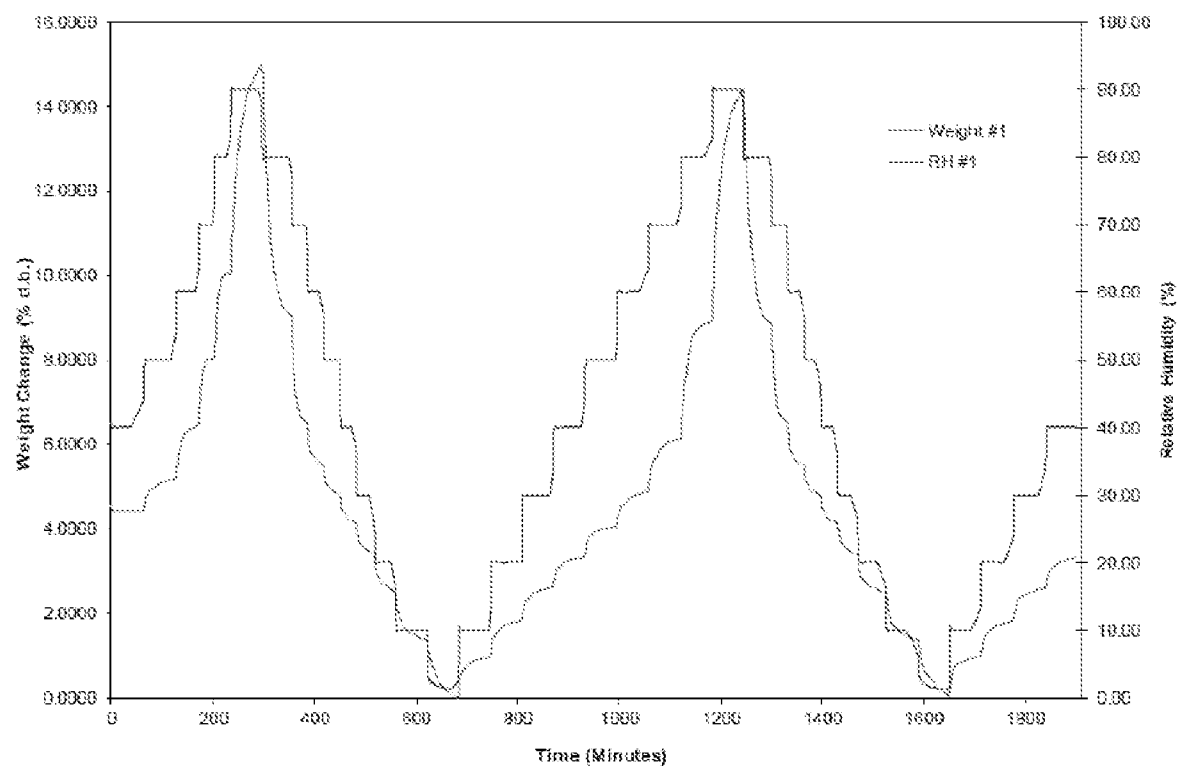


Fig. 23E

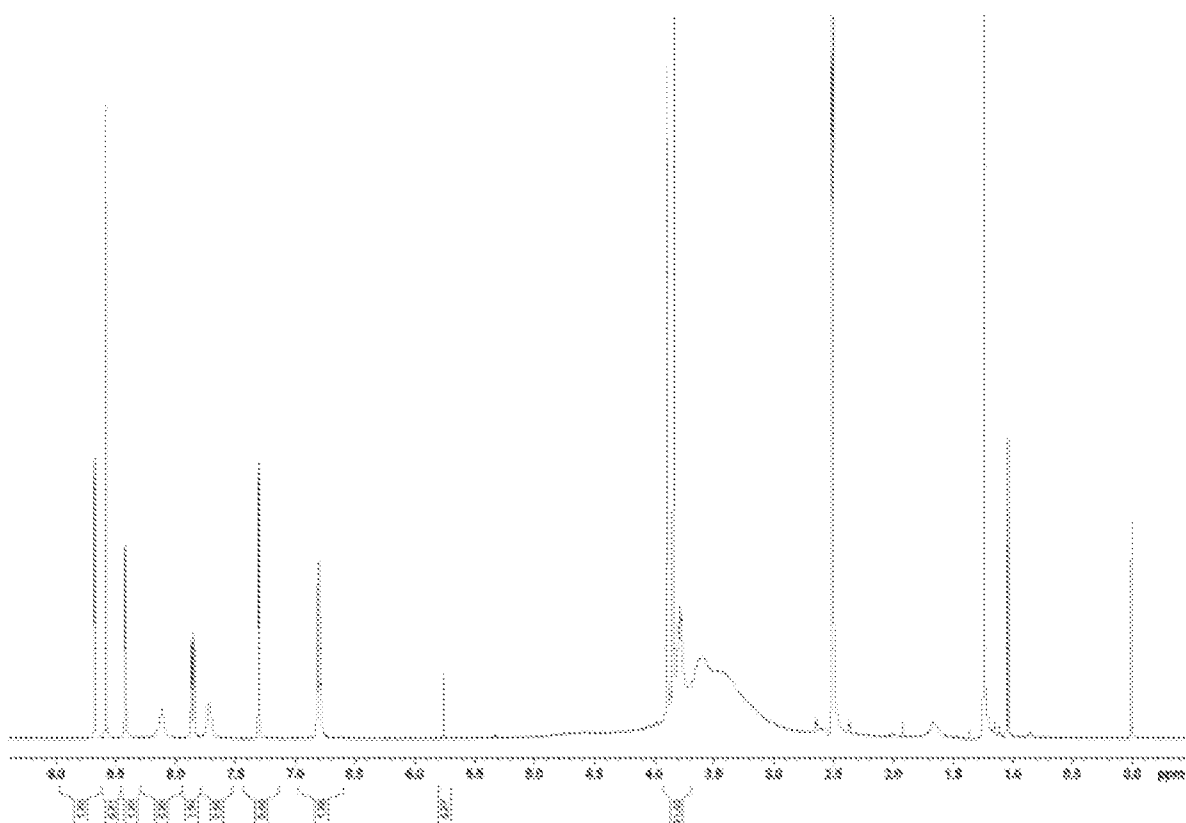


Fig. 23F

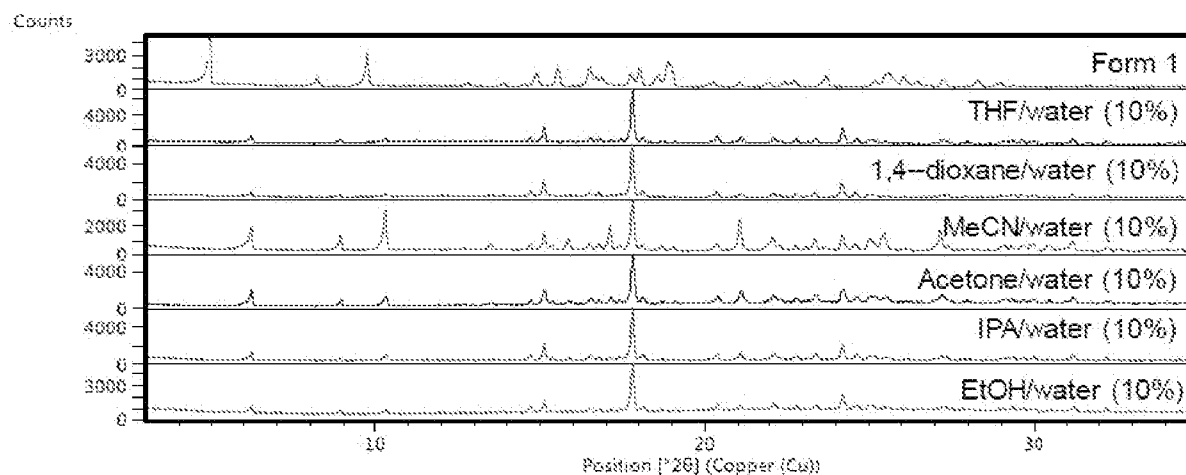


Fig. 24A

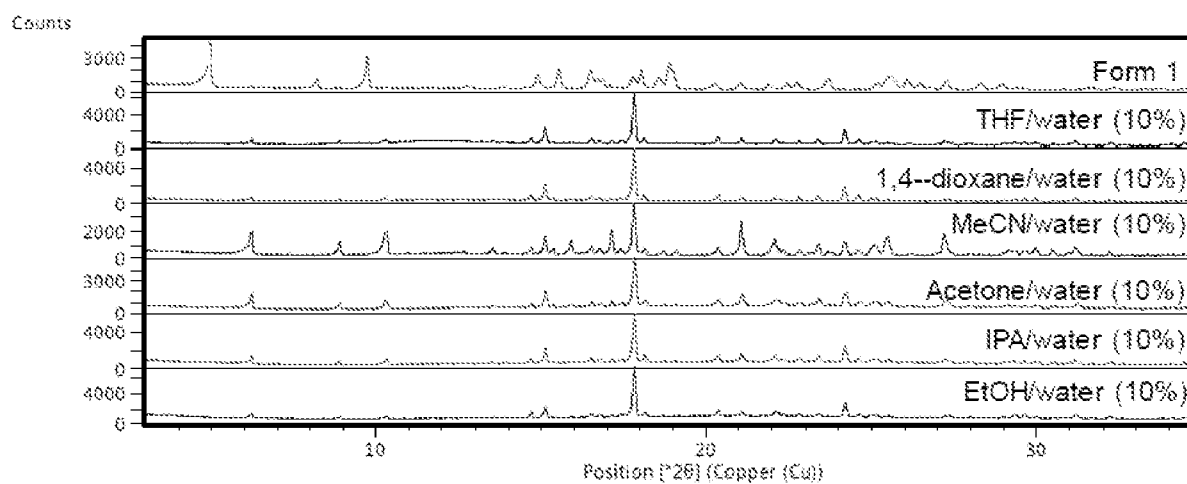


Fig. 24B

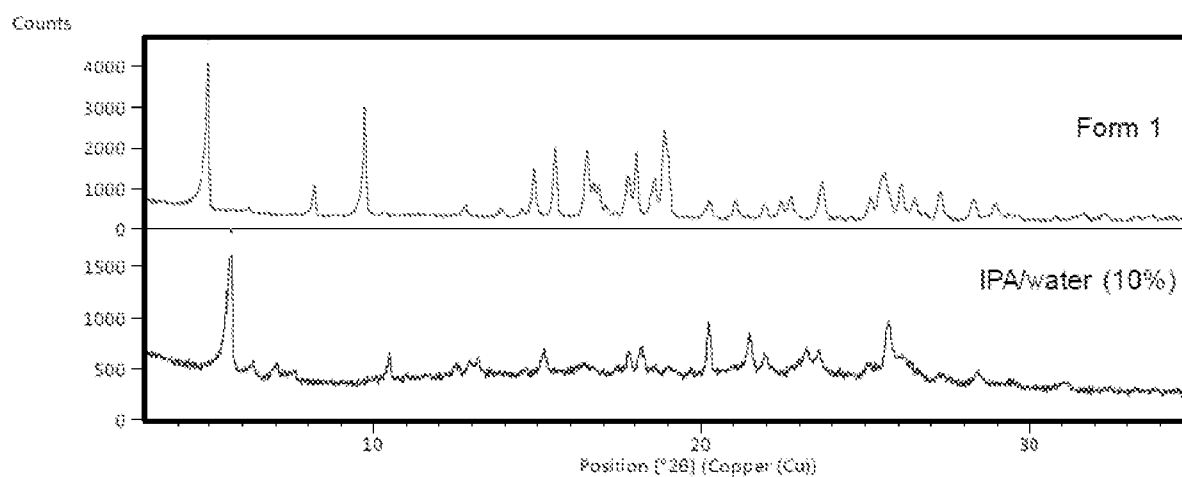


Fig. 25A

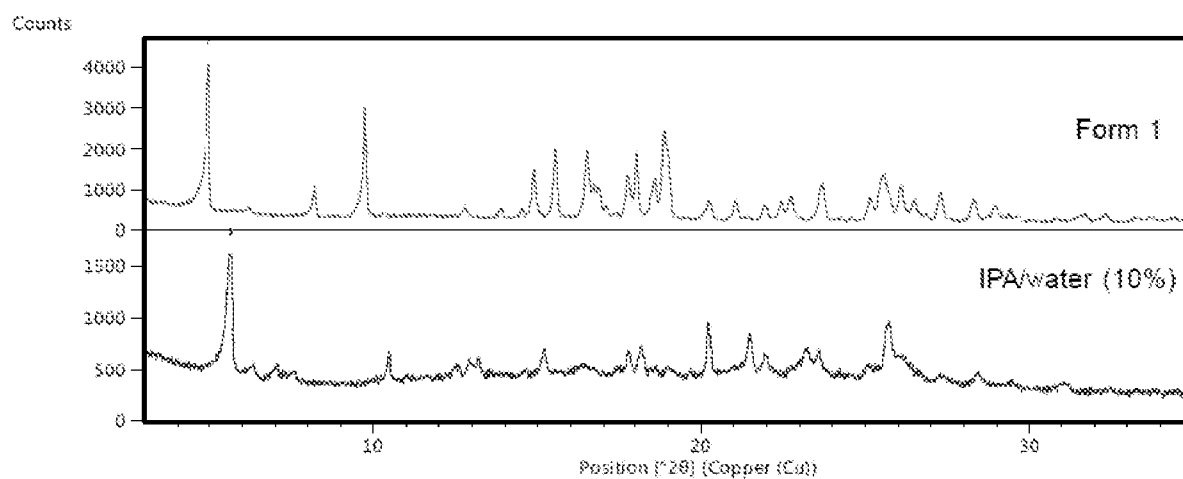


Fig. 25B

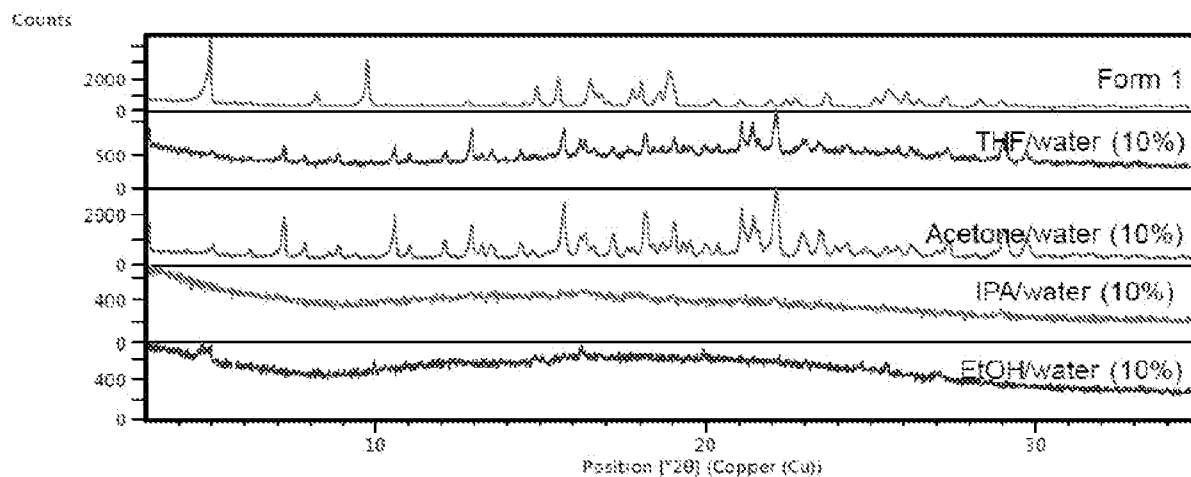


Fig. 26A

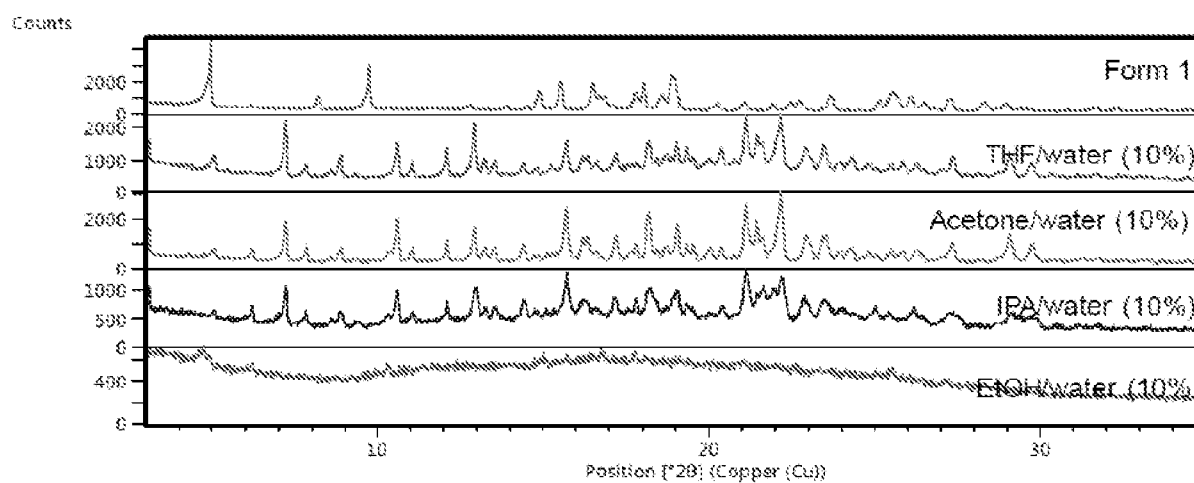


Fig. 26B

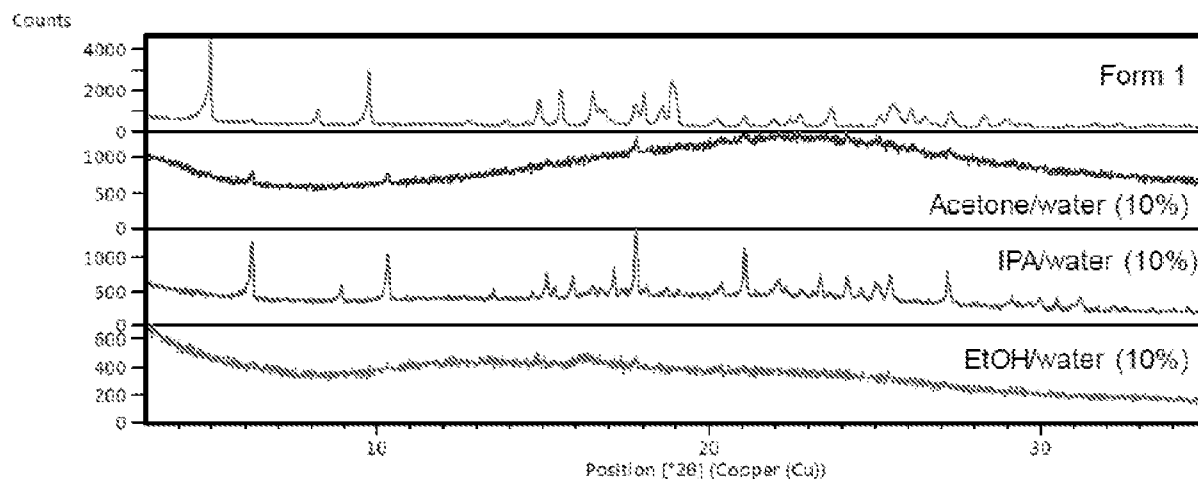


Fig. 27A

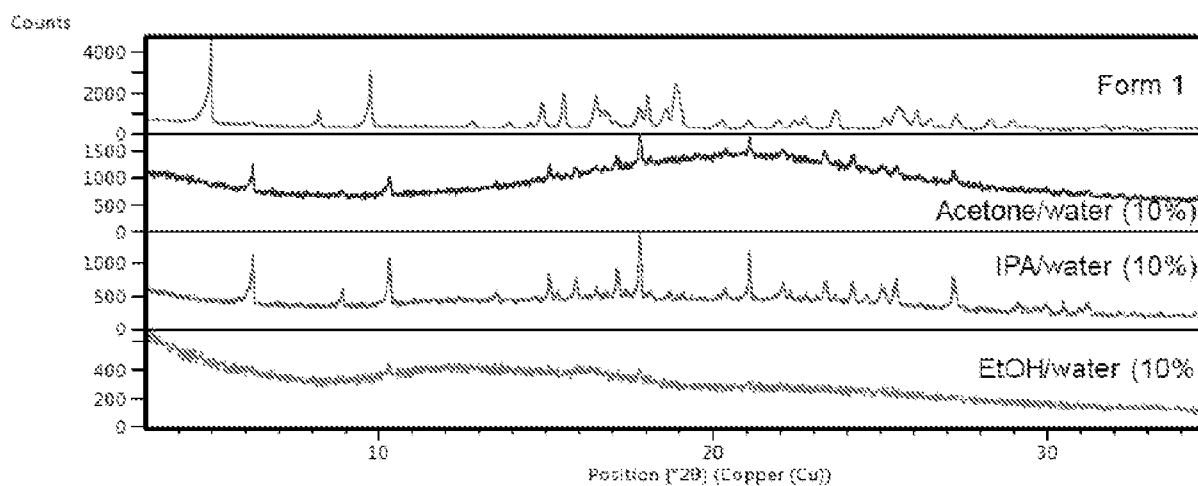


Fig. 27B

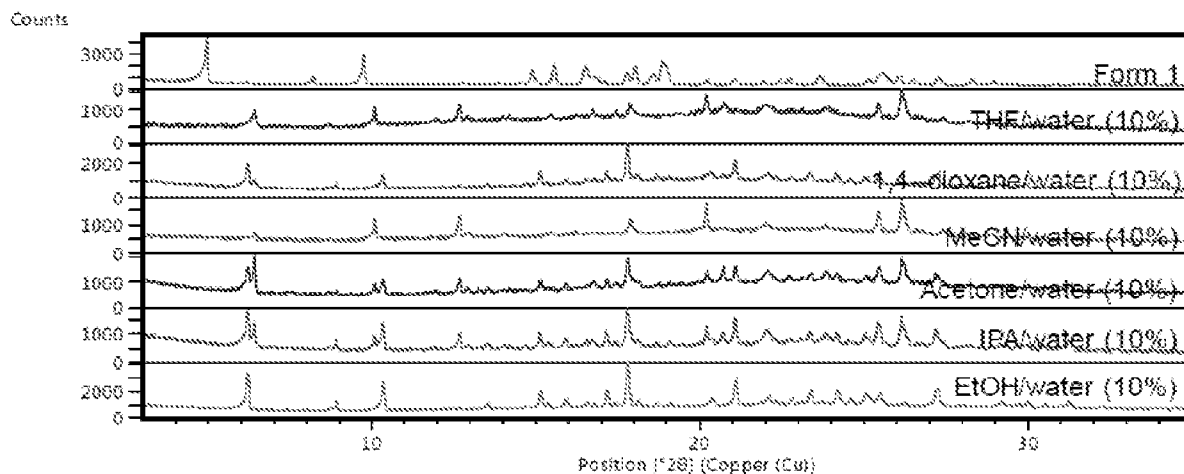


Fig. 28A

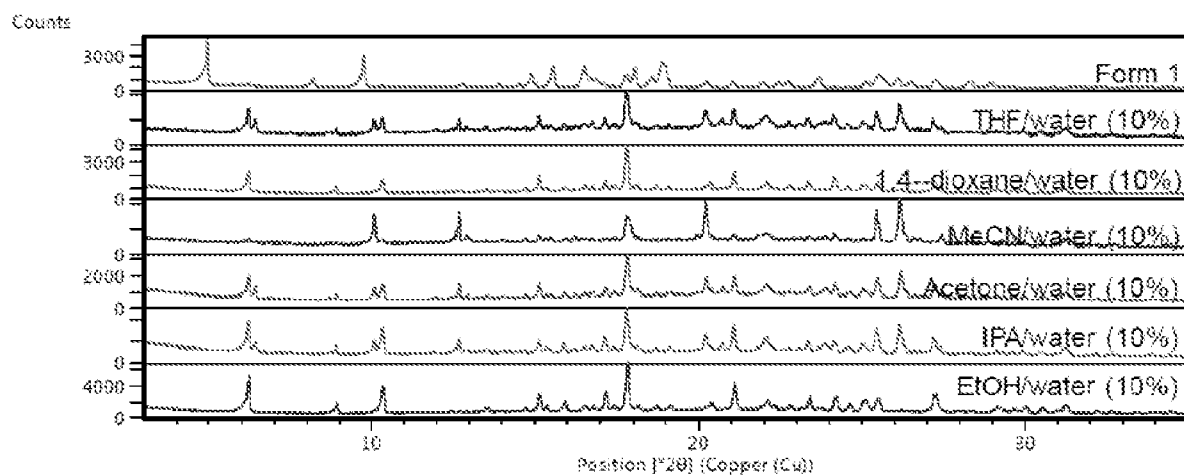


Fig. 28B

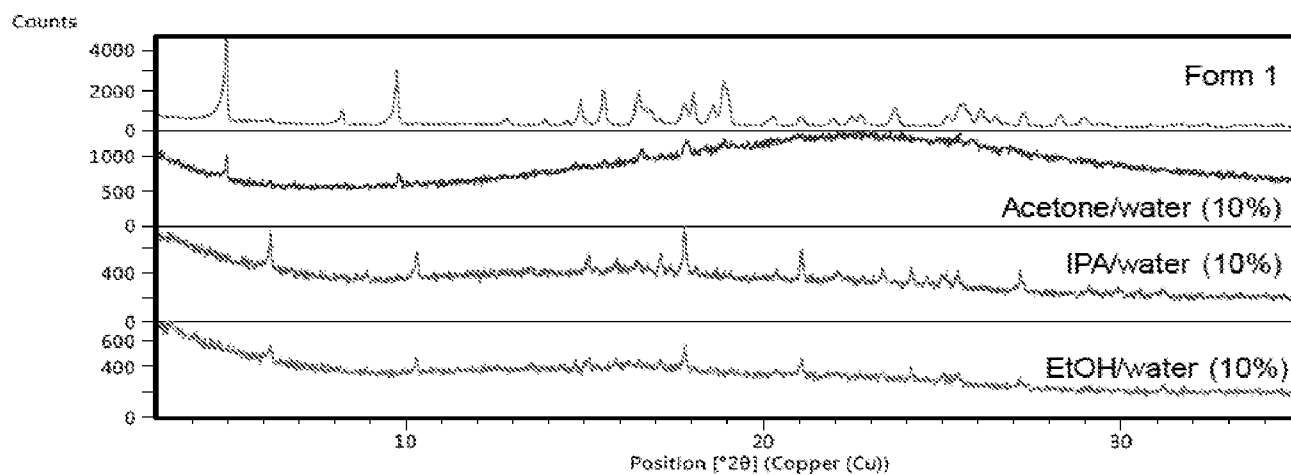


Fig. 29A

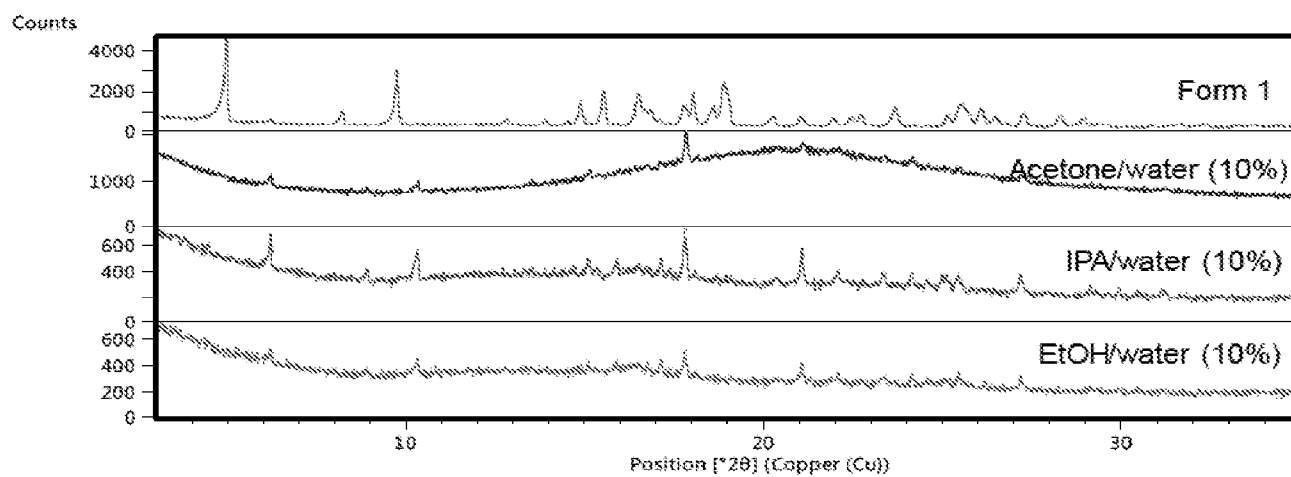


Fig. 29B

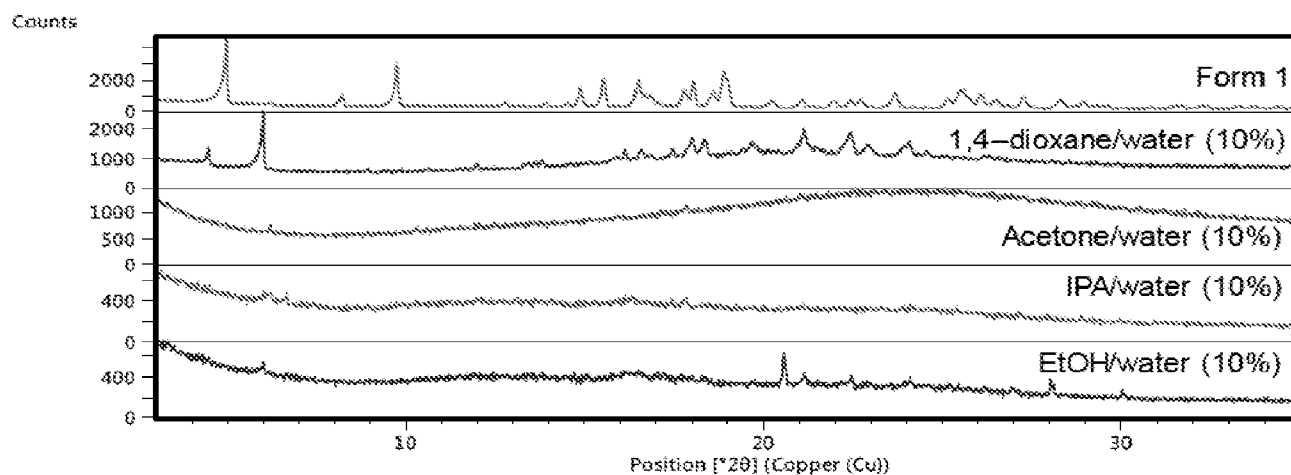


Fig. 30A

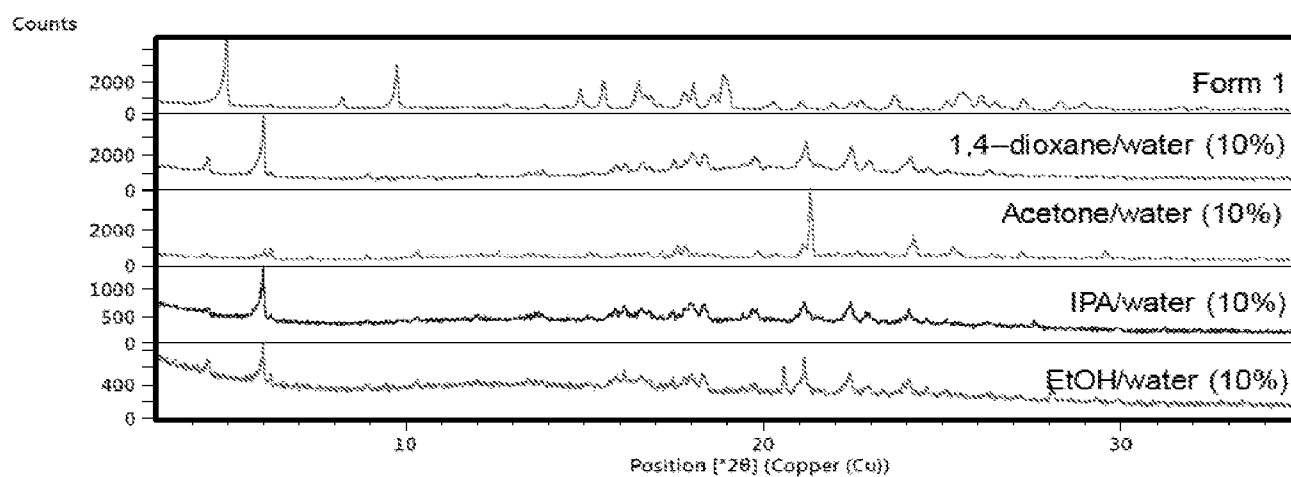


Fig. 30B

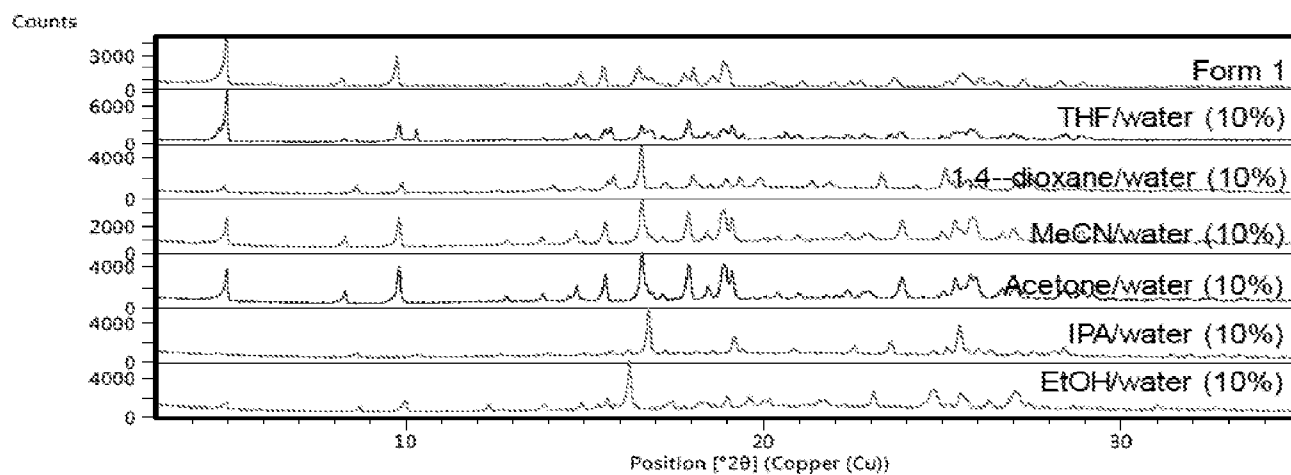


Fig. 31A

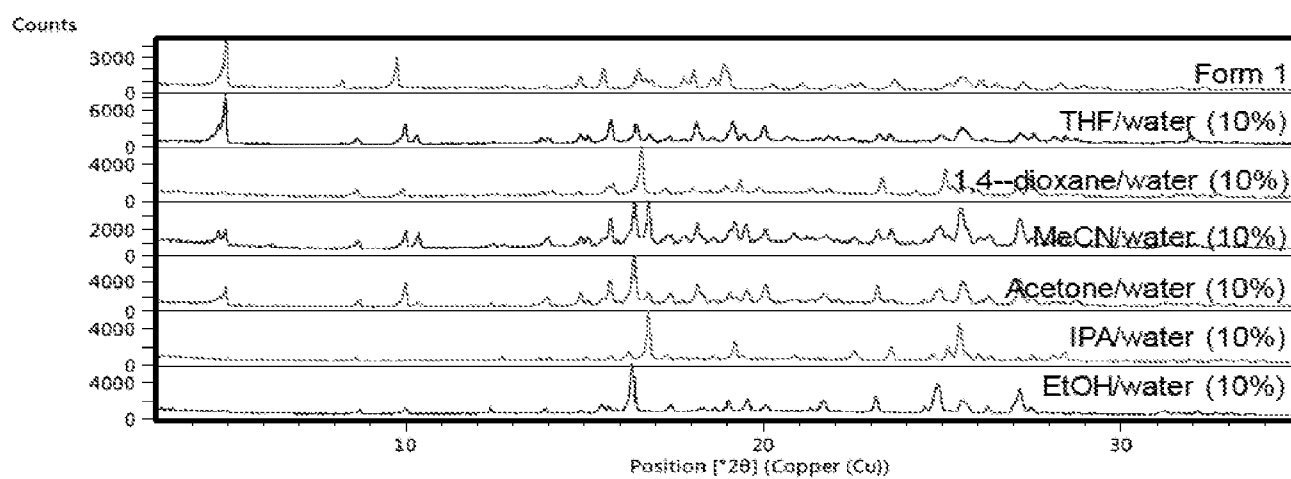


Fig. 31B

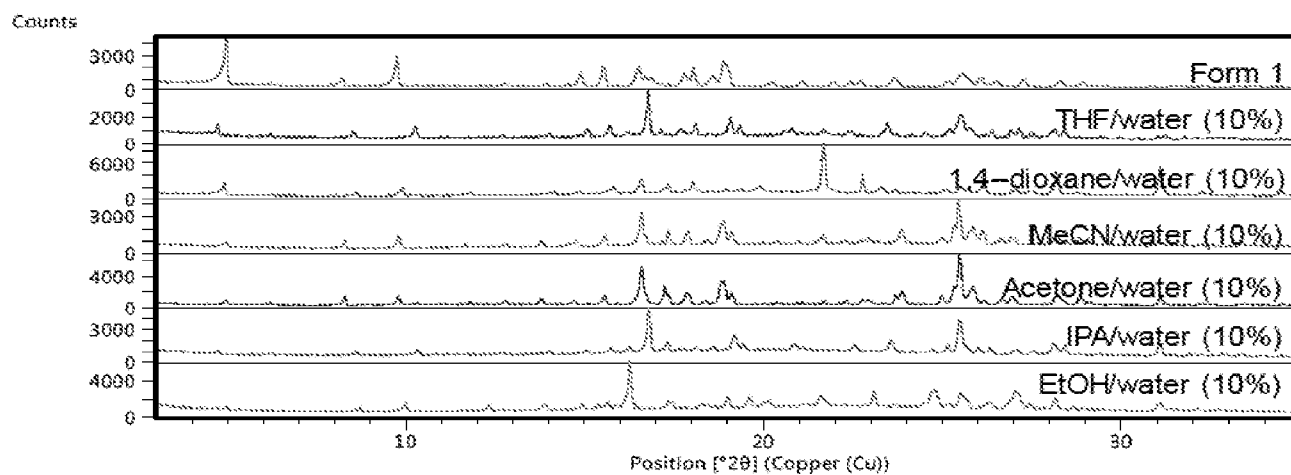


Fig. 32A

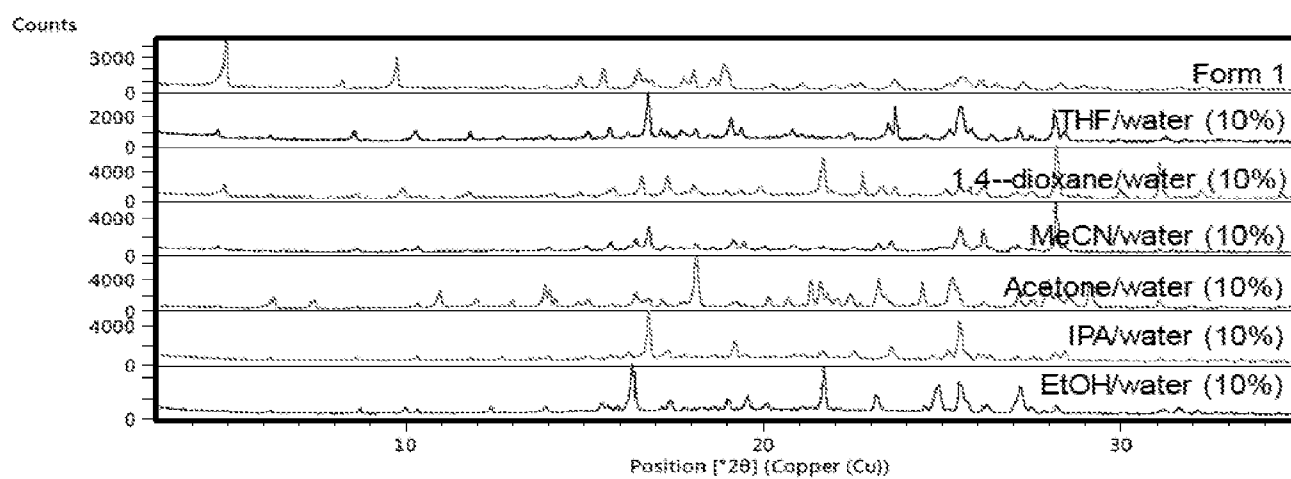


Fig. 32B

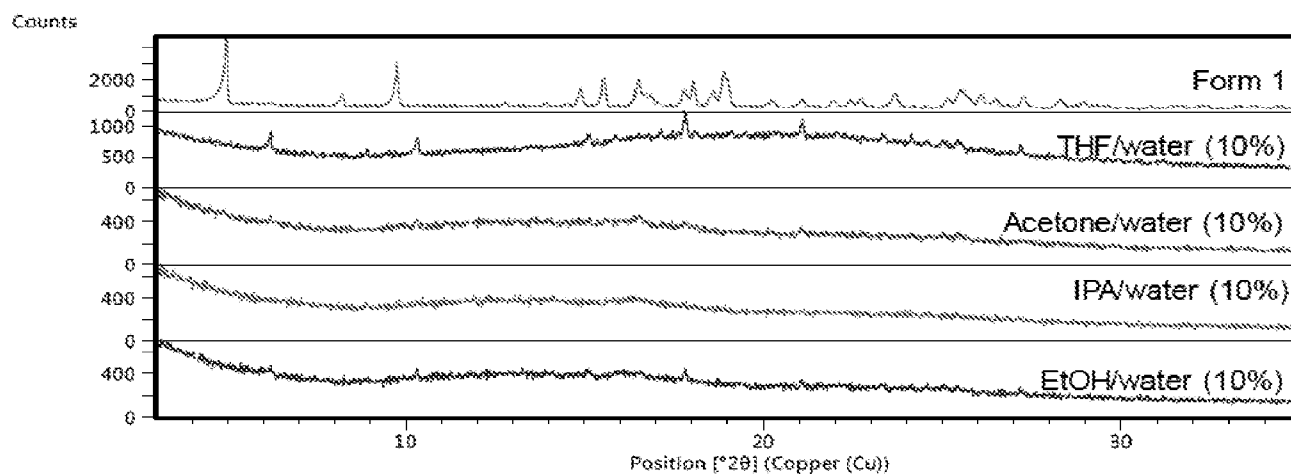


Fig. 33A

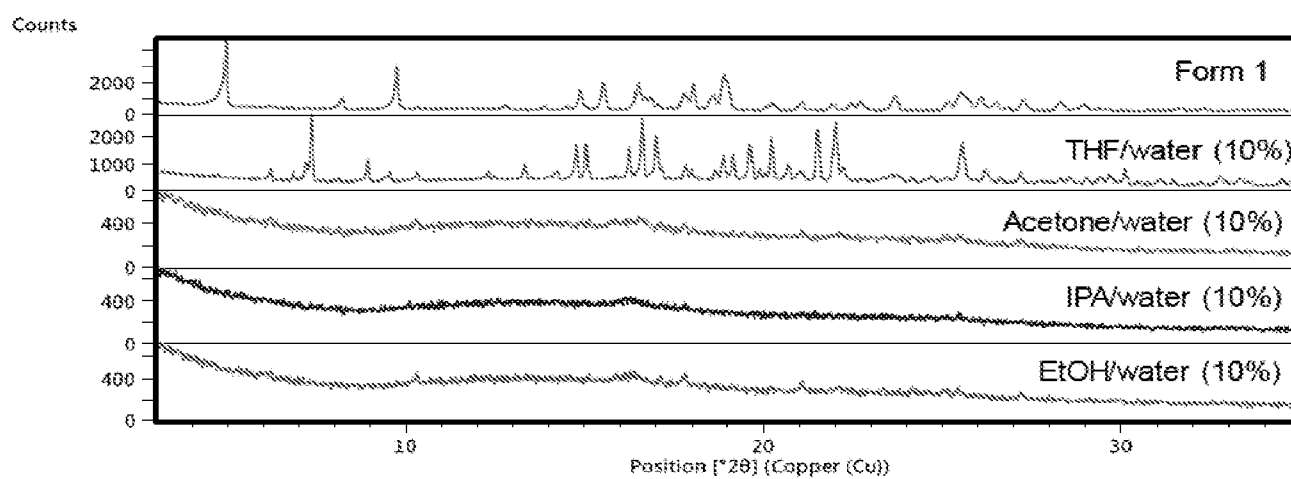


Fig. 33B

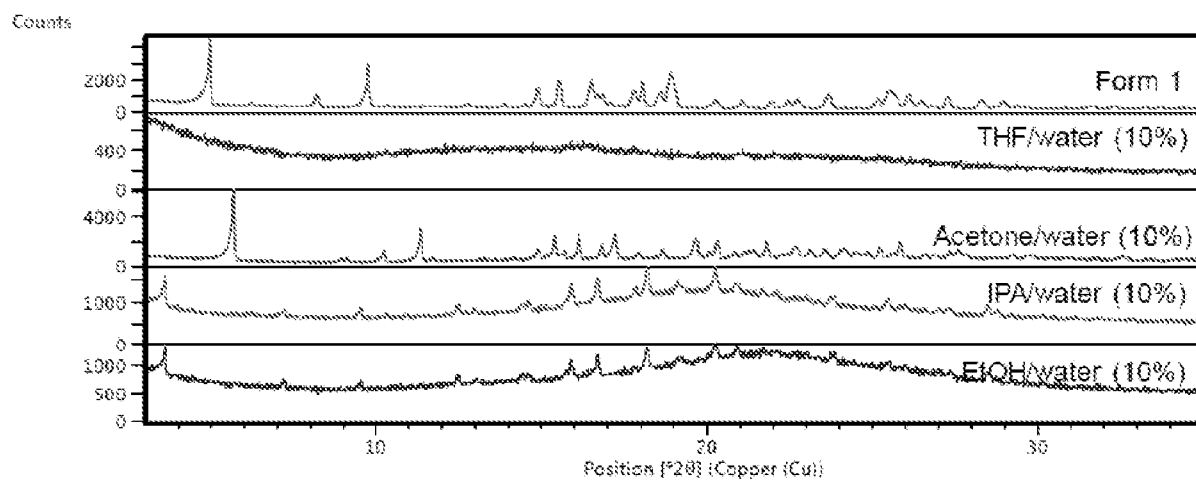


Fig. 34A

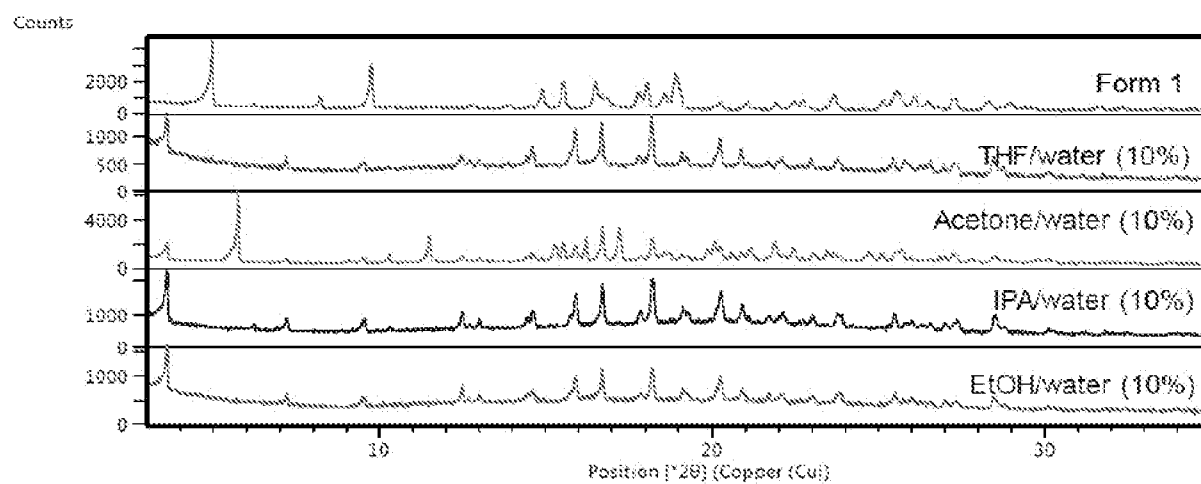


Fig. 34B

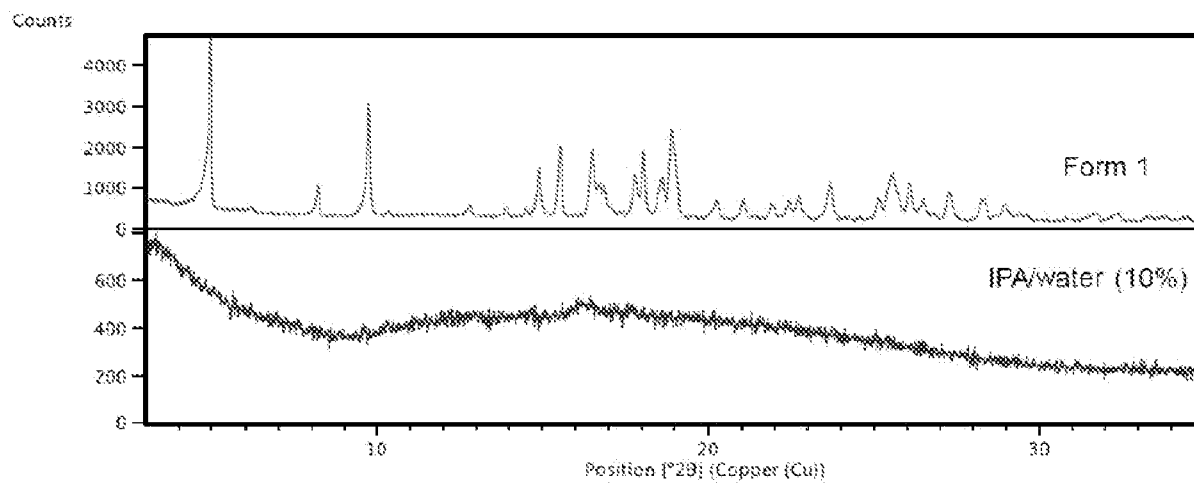


Fig. 35A

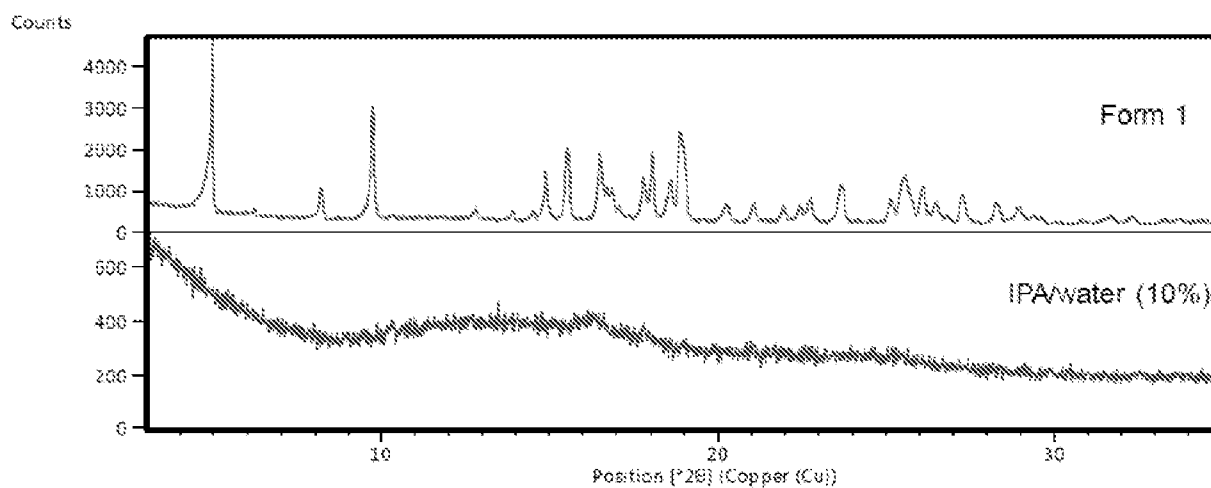


Fig. 35B

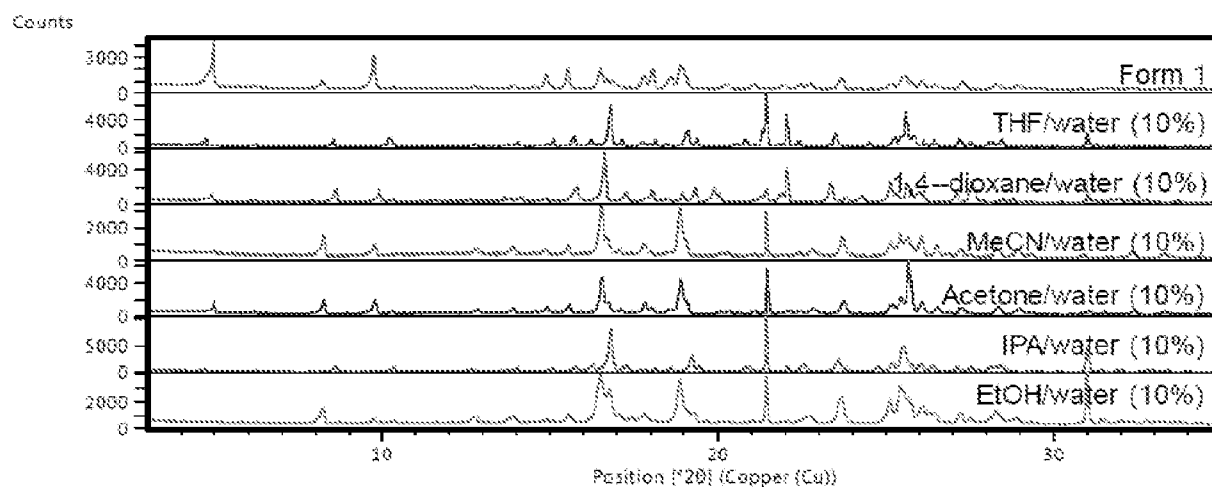


Fig. 36A

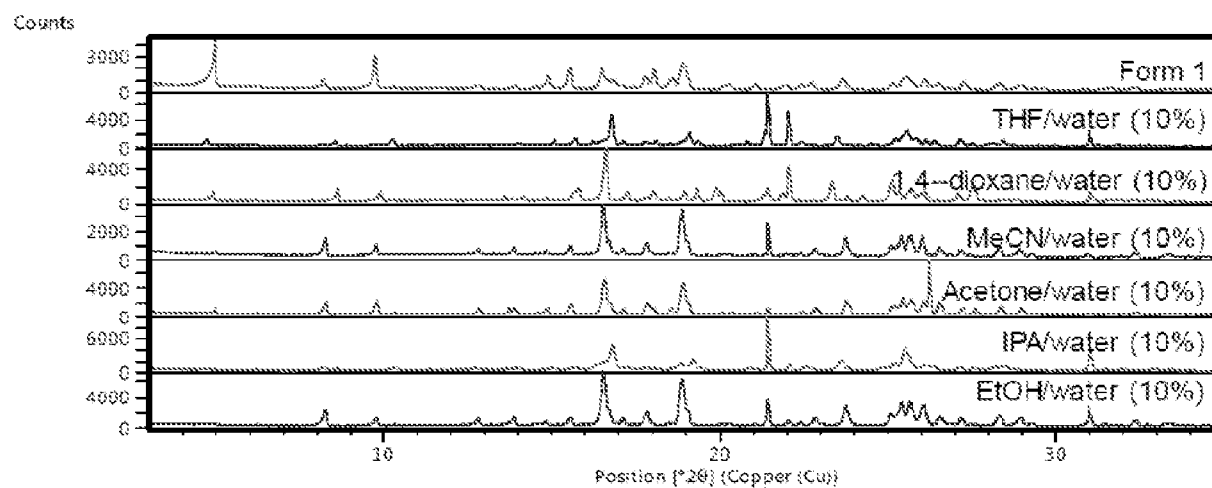


Fig. 36B

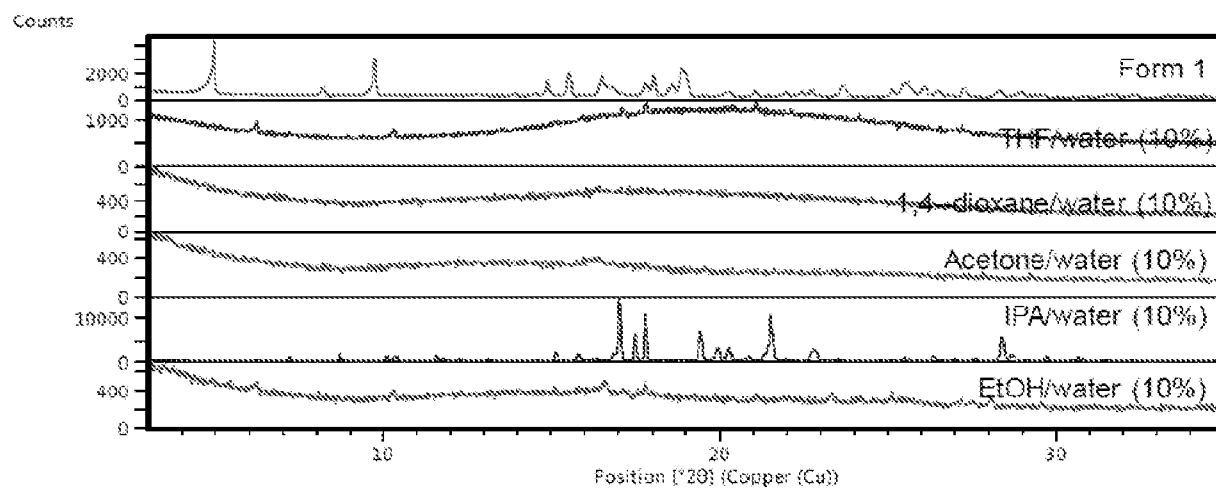


Fig. 37A

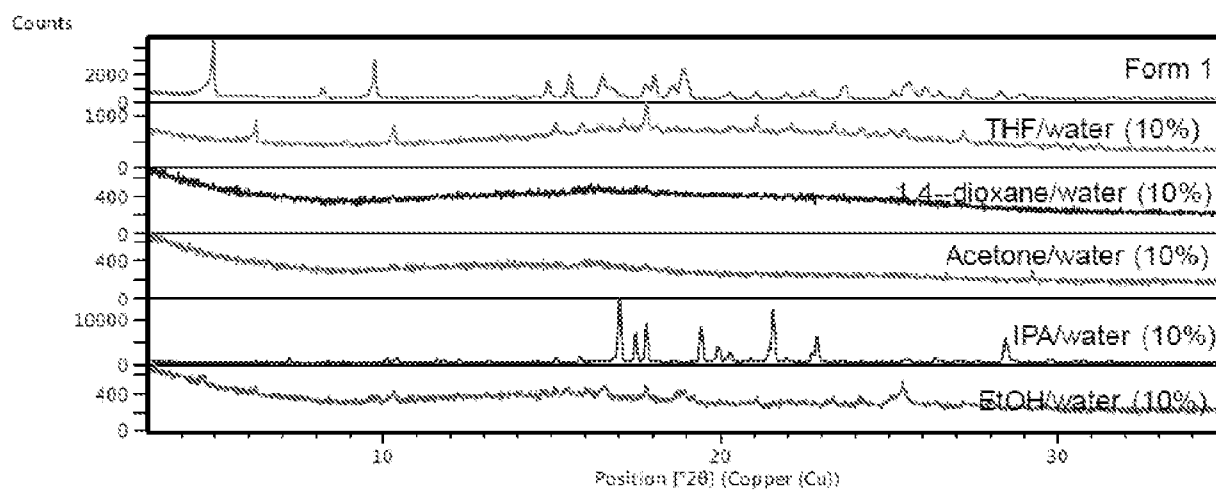


Fig. 37B

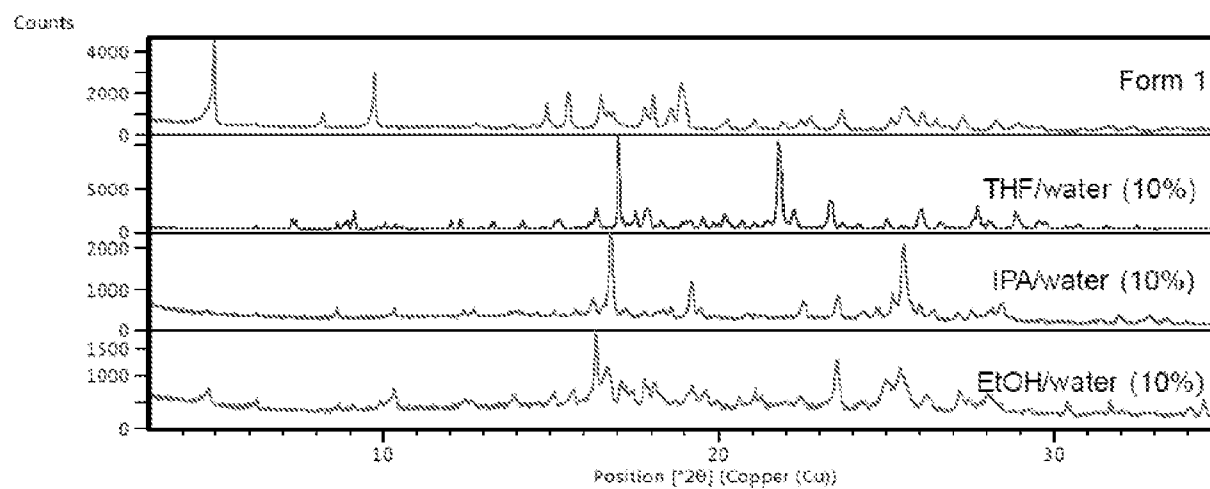


Fig. 38A

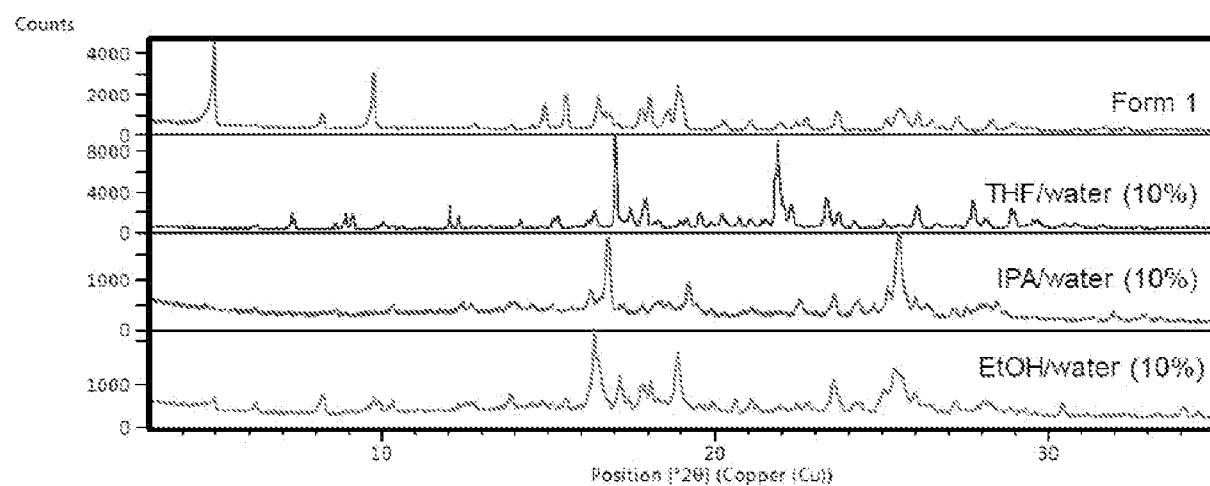


Fig. 38B

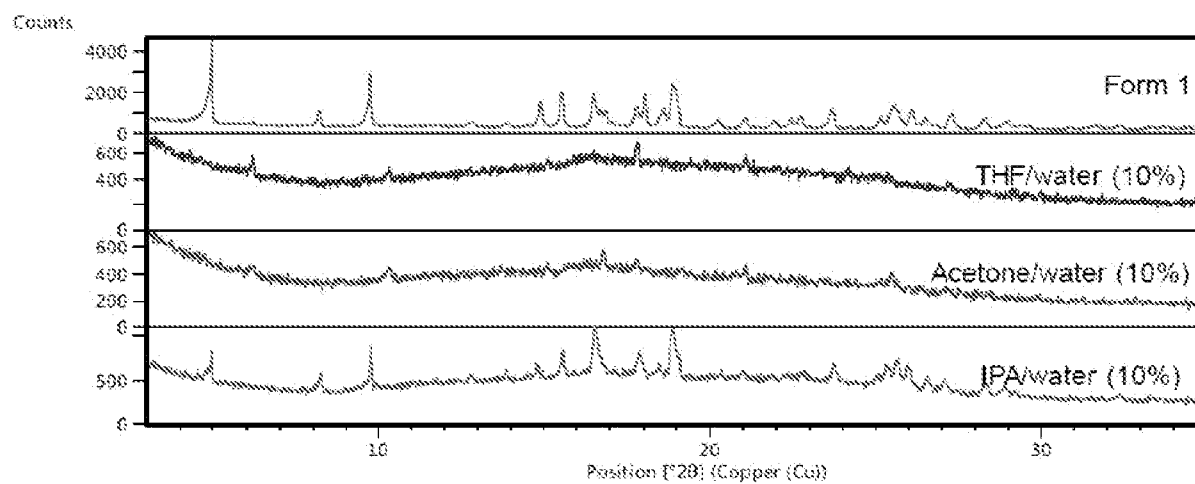


Fig. 39A

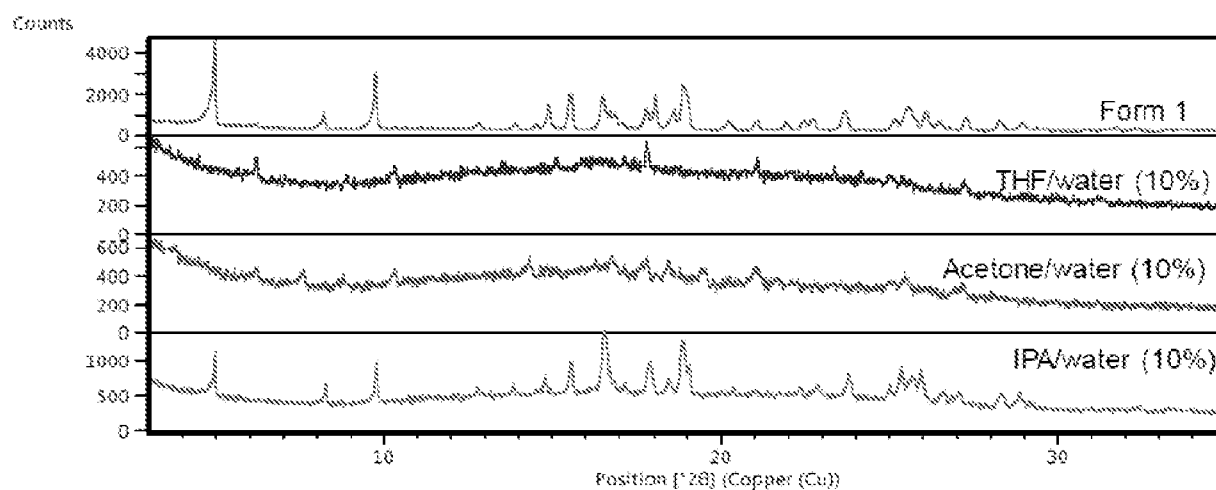


Fig. 39B

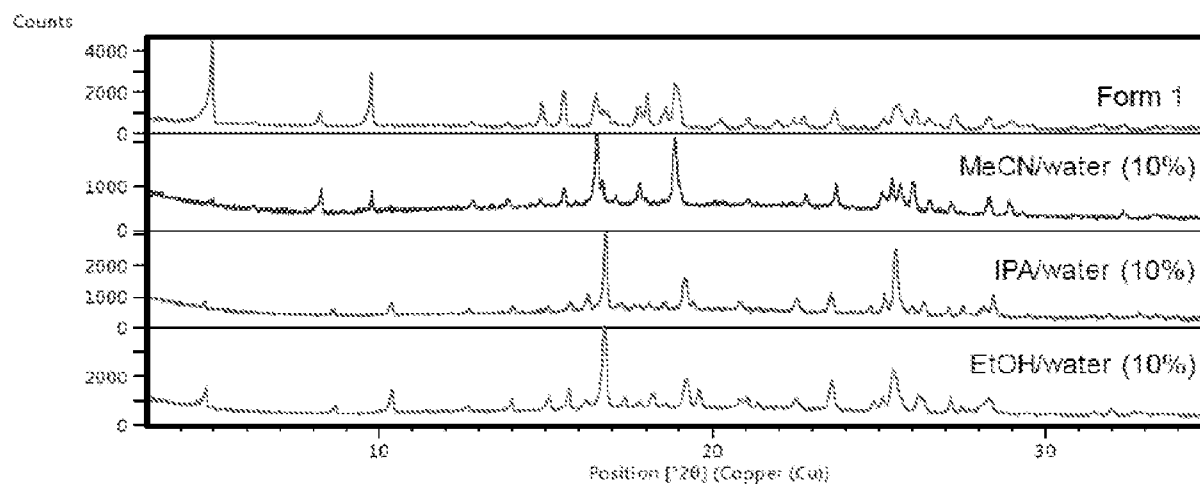


Fig. 40A

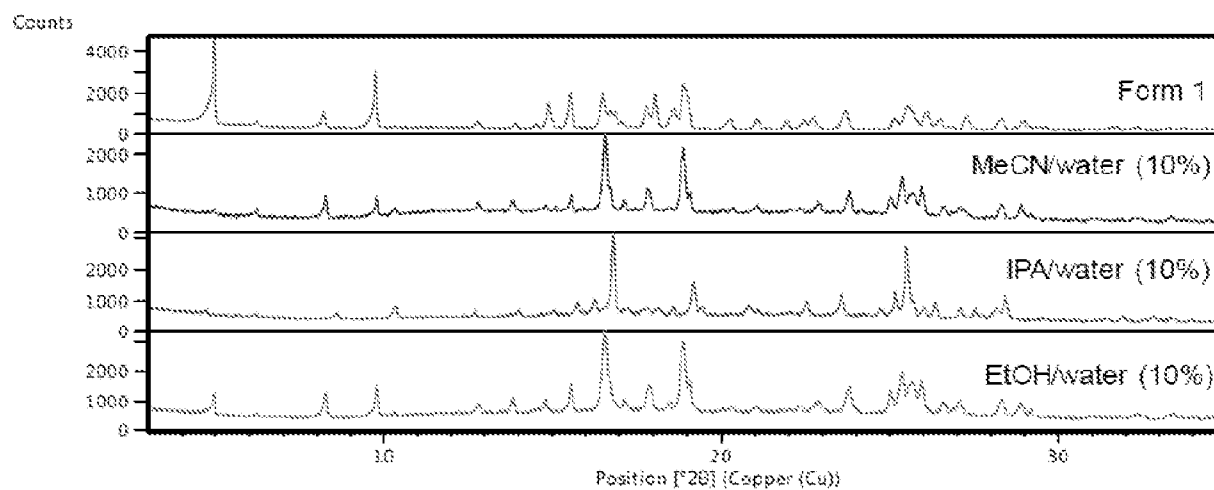


Fig. 40B

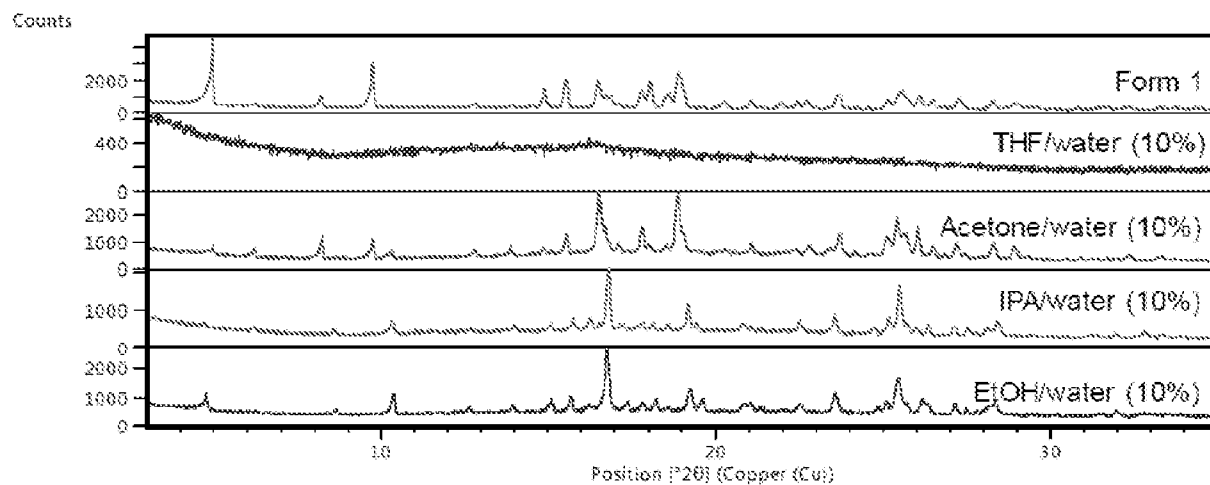


Fig. 41A

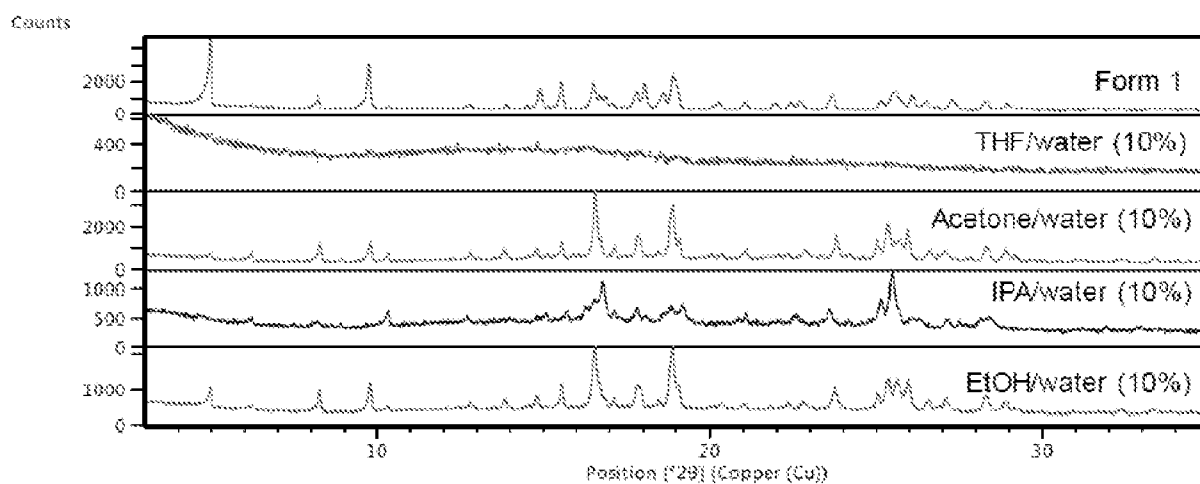


Fig. 41B

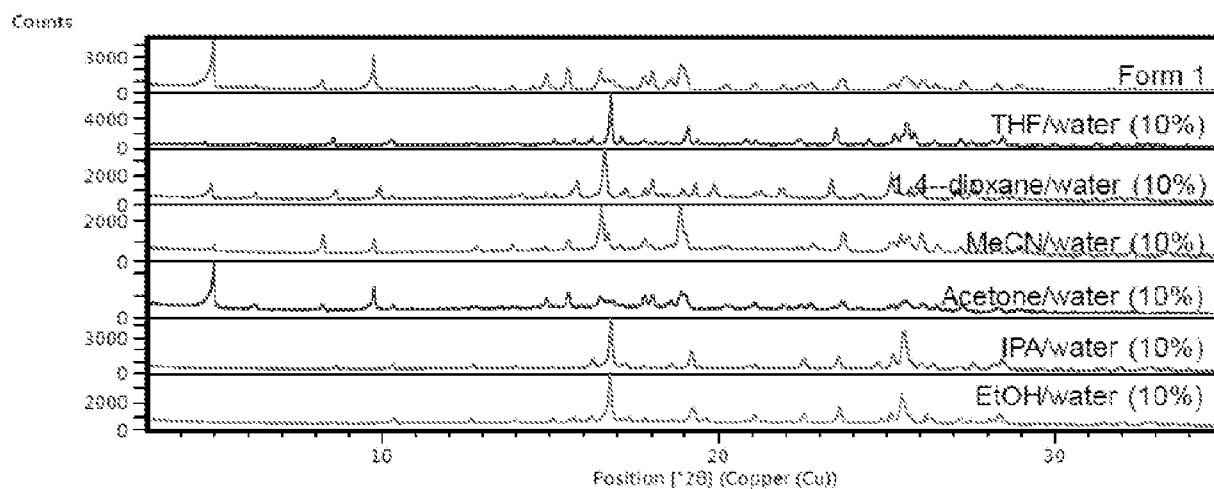


Fig. 42A

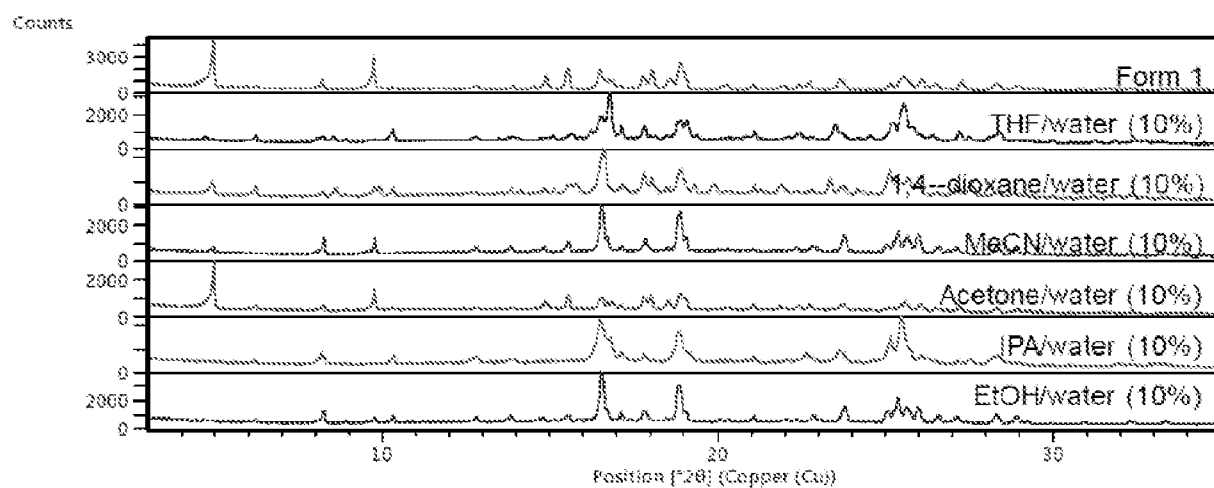


Fig. 42B

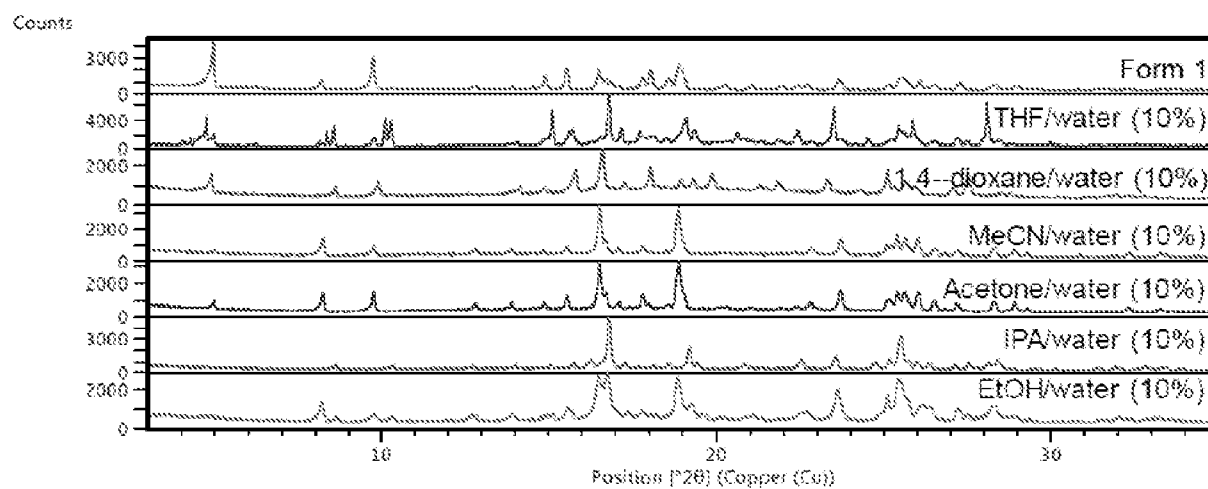


Fig. 43A

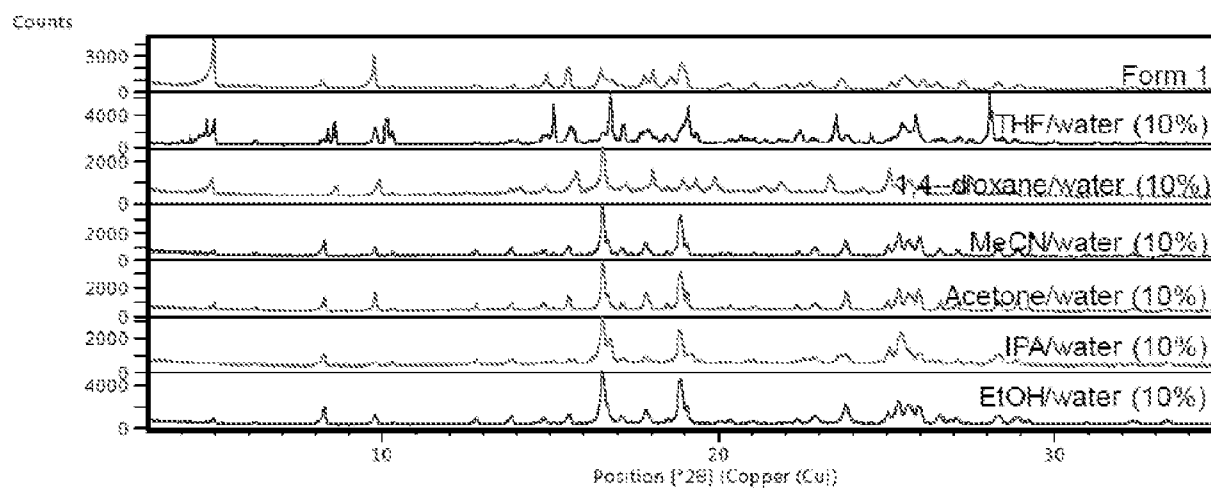


Fig. 43B

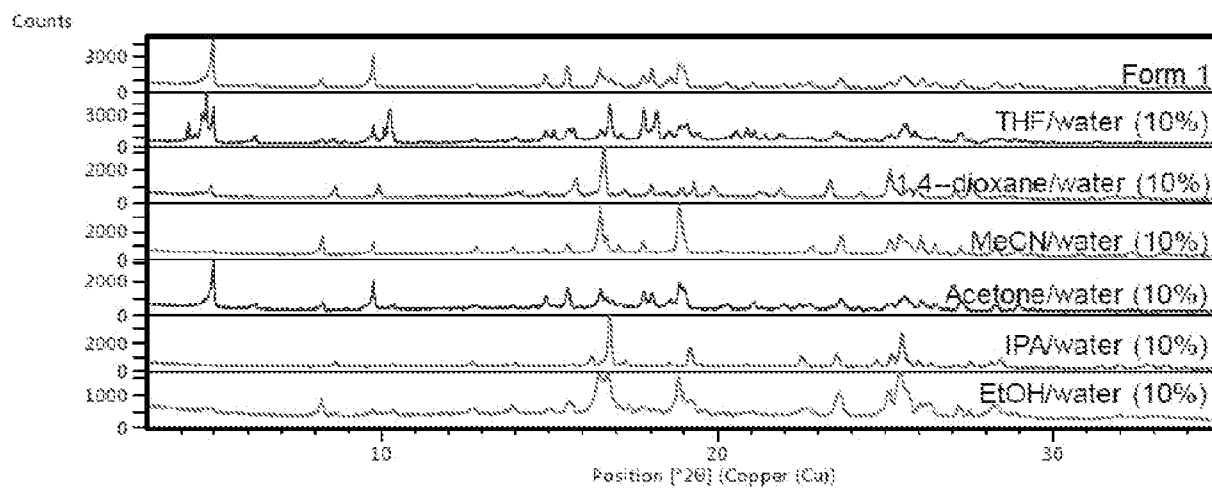


Fig. 44A

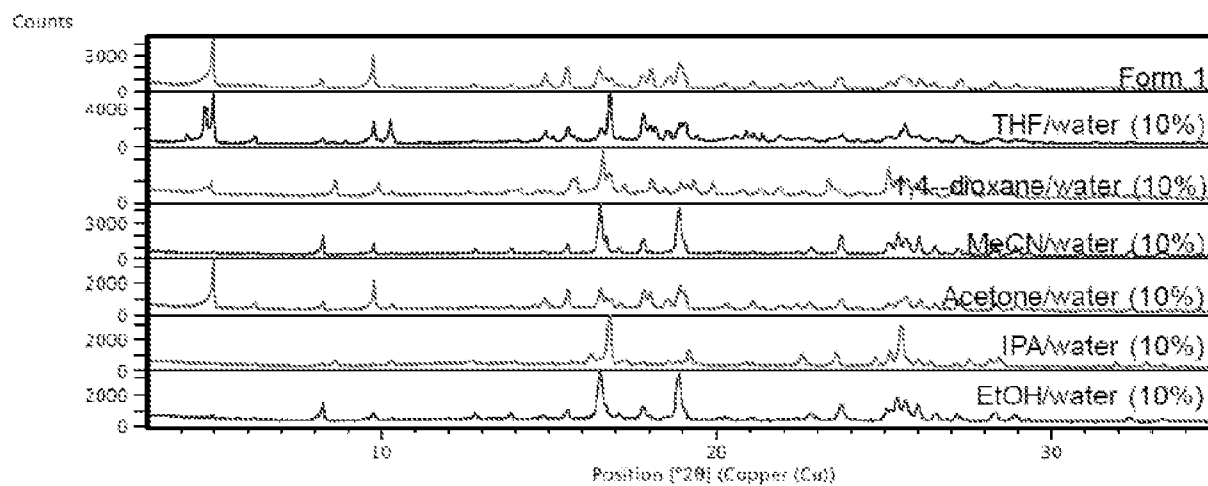


Fig. 44B

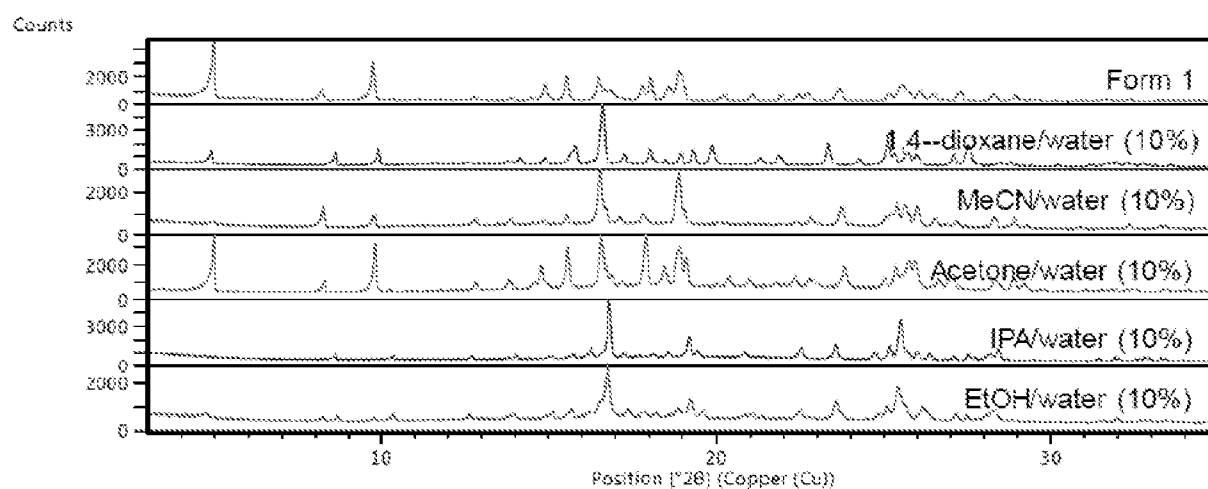


Fig. 45A

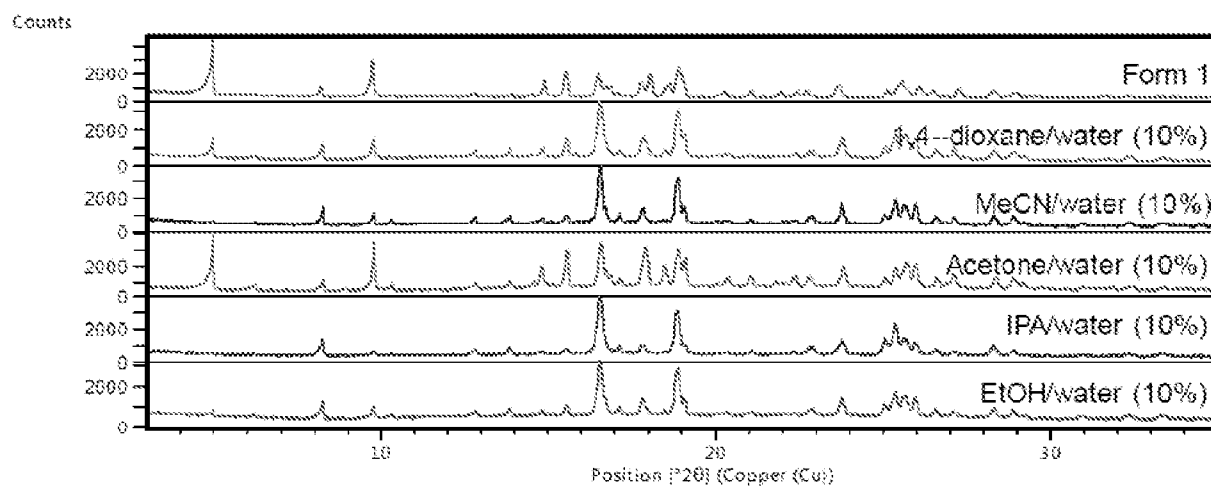


Fig. 45B

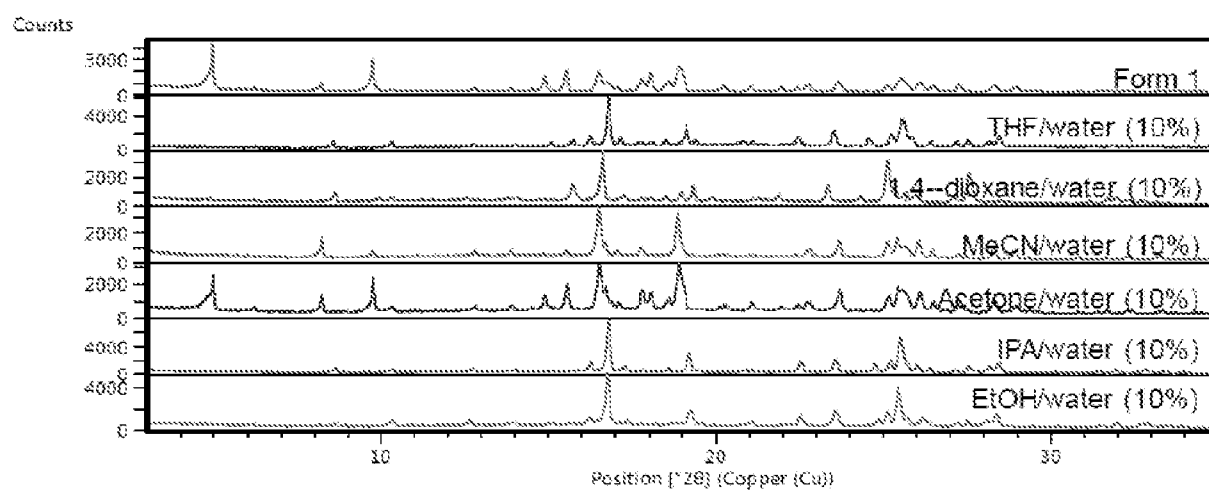


Fig. 46A

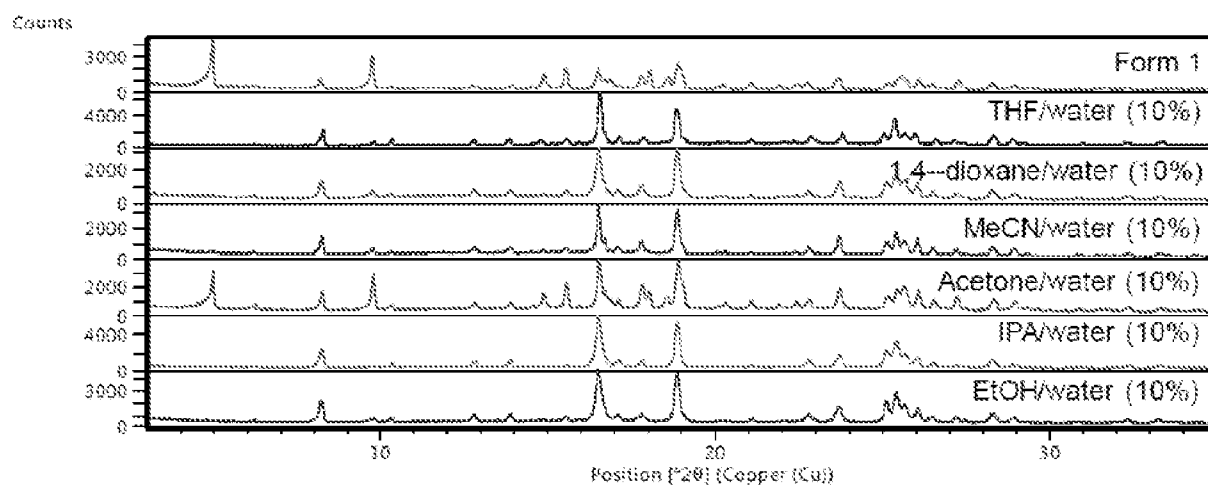


Fig. 46B

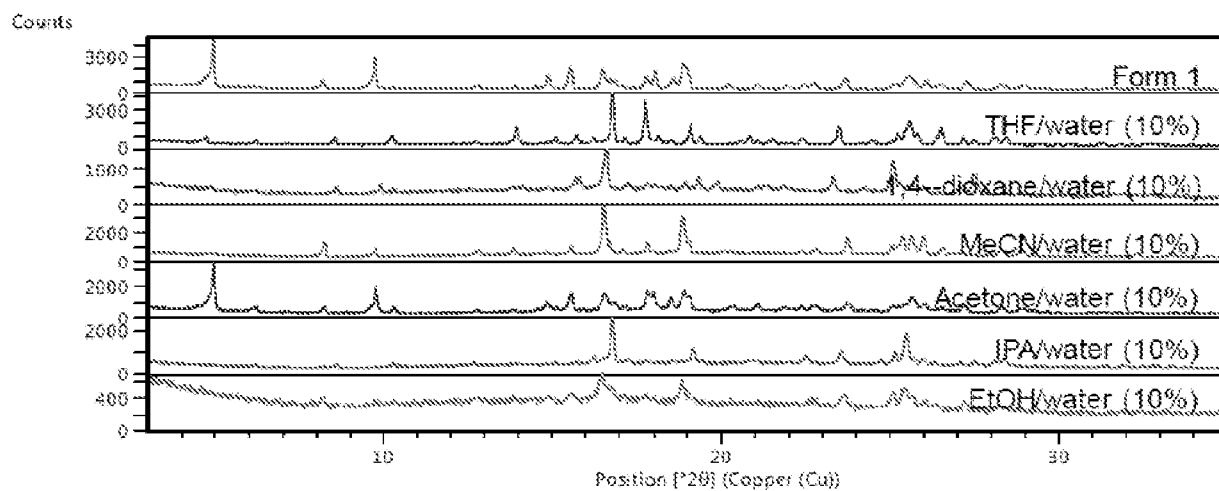


Fig. 47A

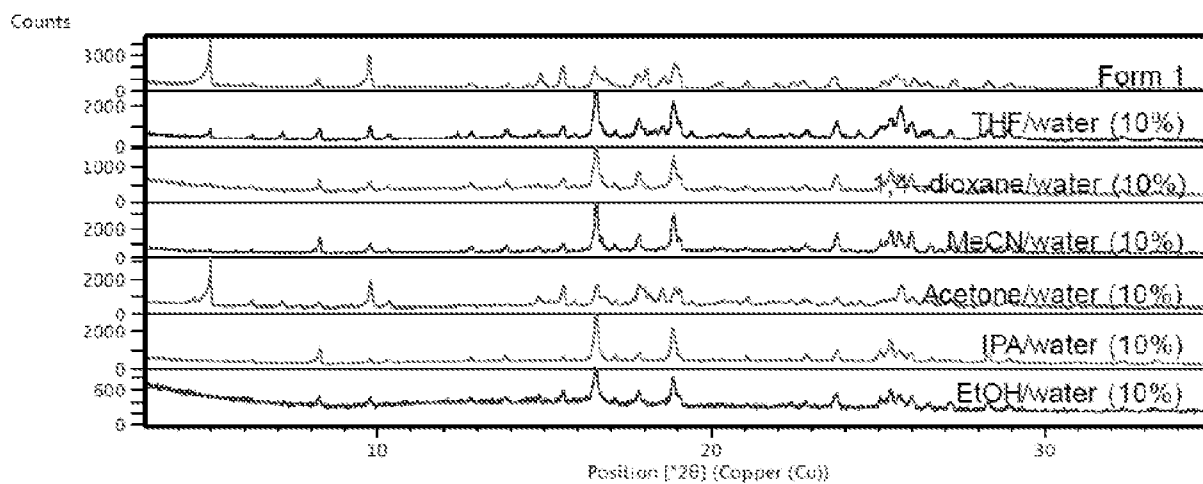


Fig. 47B

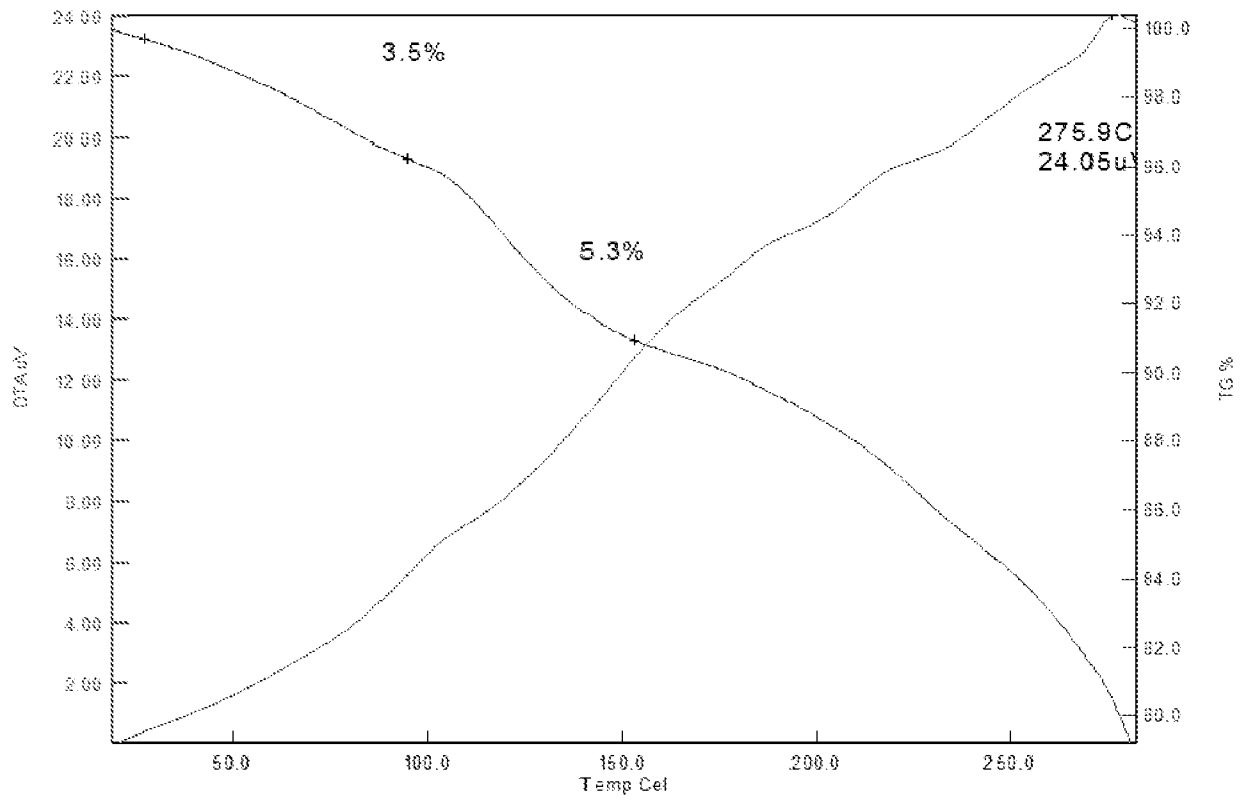


Fig. 48

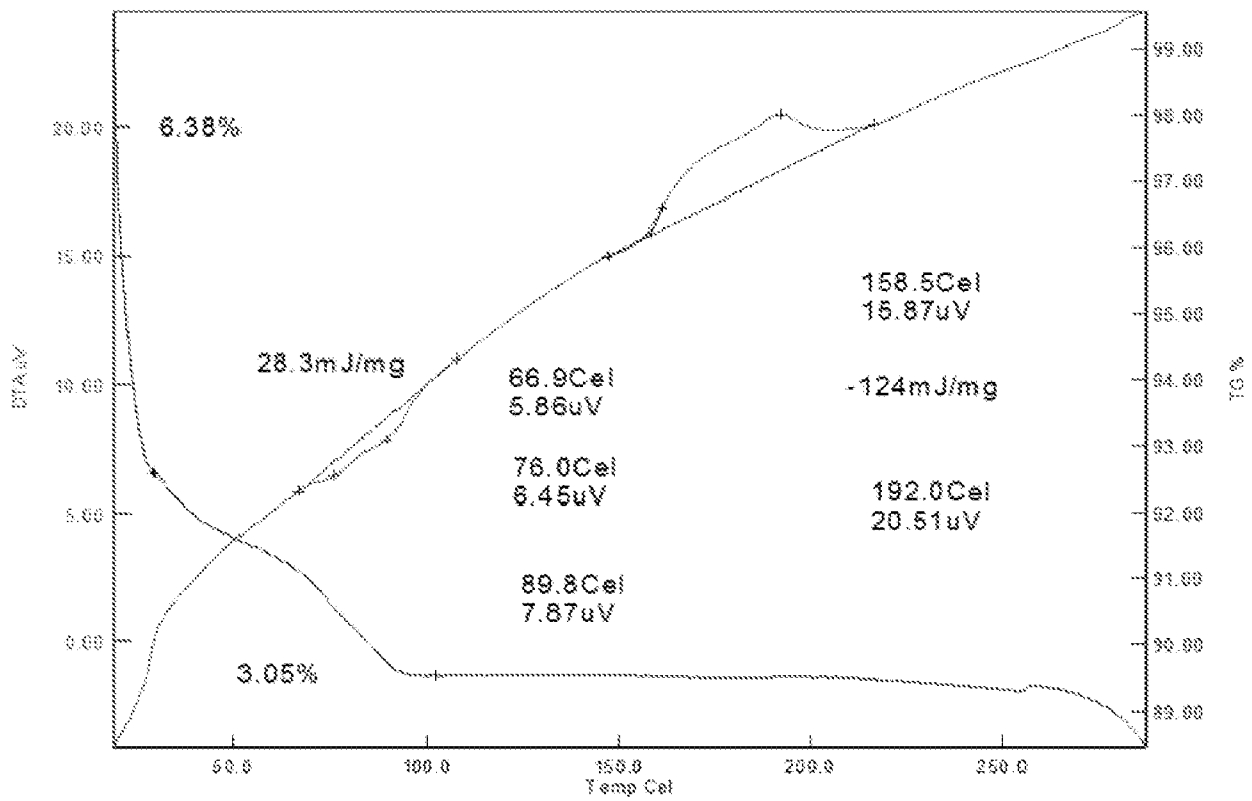


Fig. 49

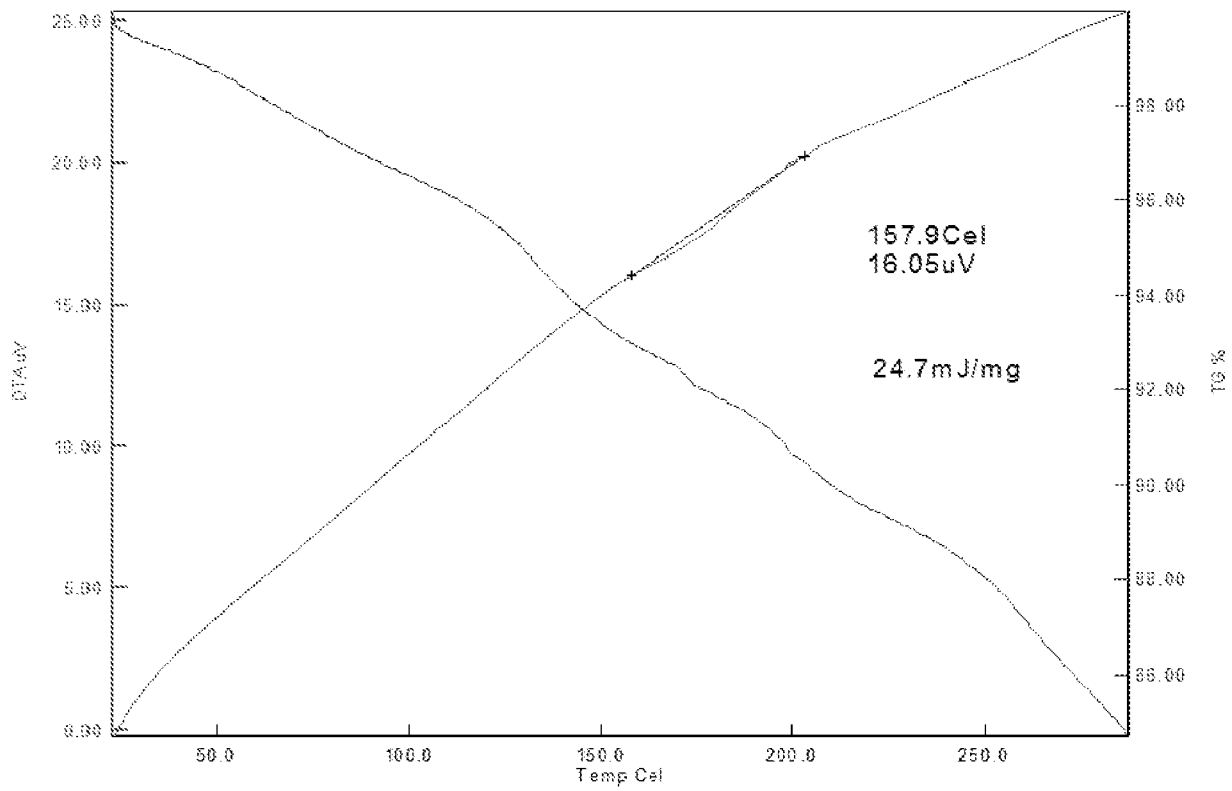


Fig. 50

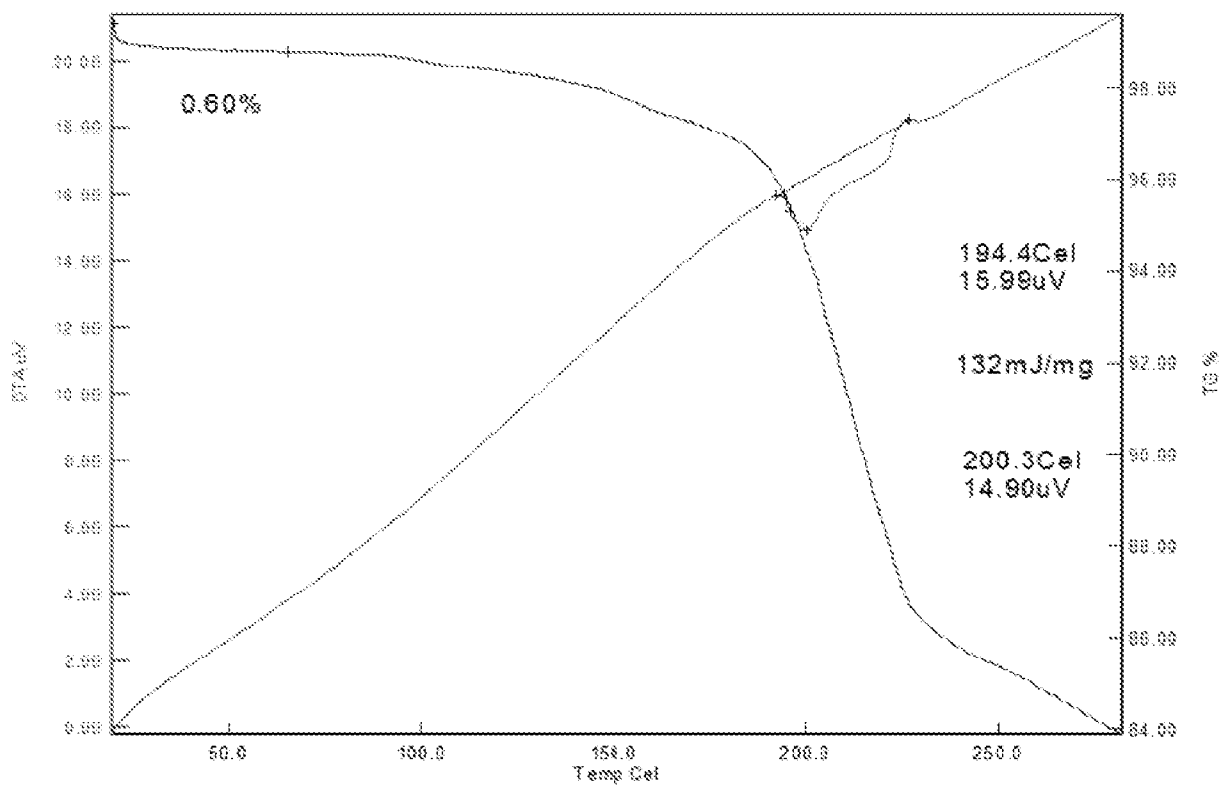


Fig. 51

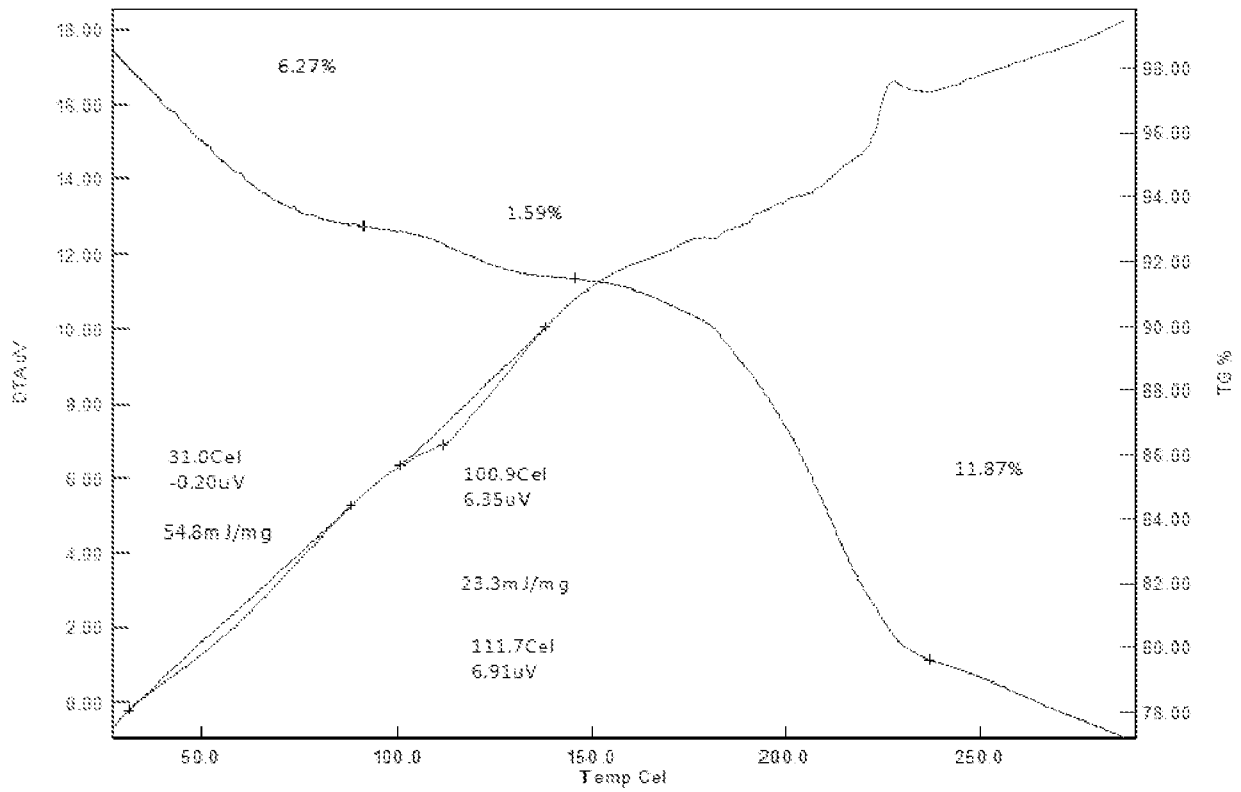


Fig. 52

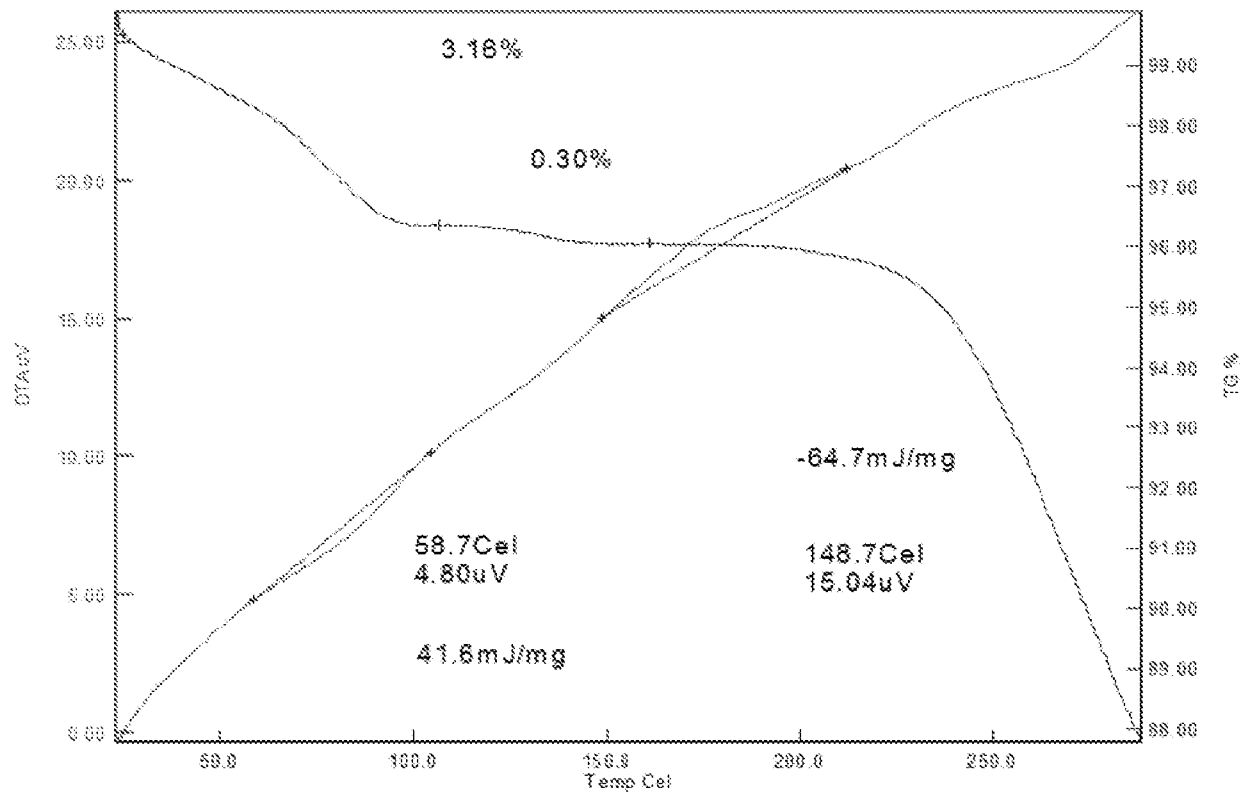


Fig. 53

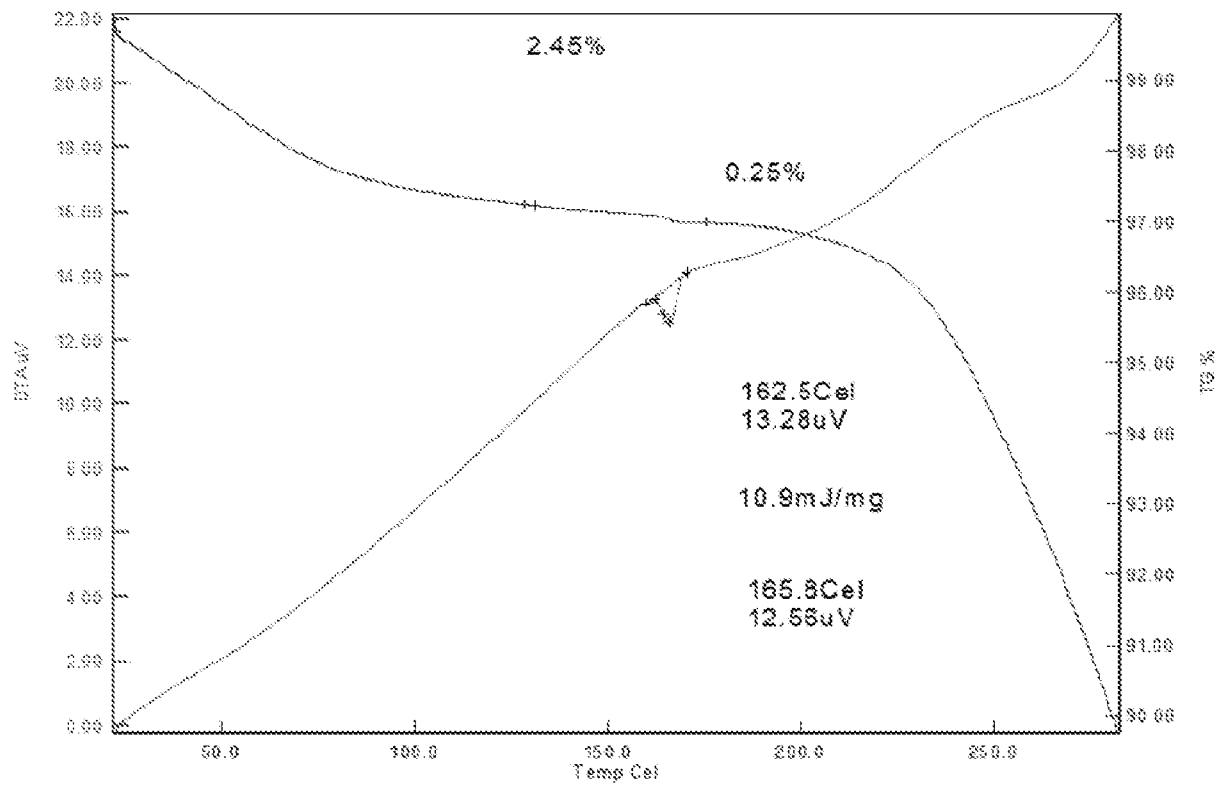


Fig. 54

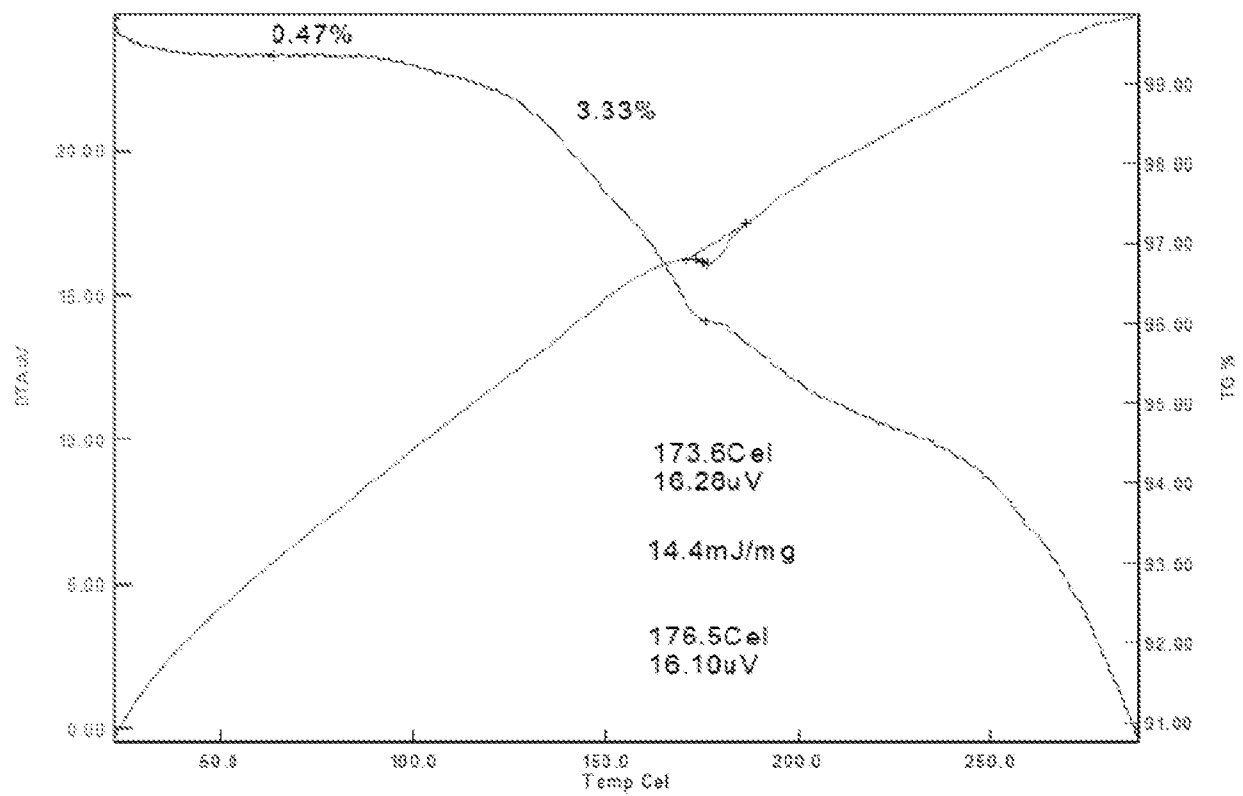


Fig. 55

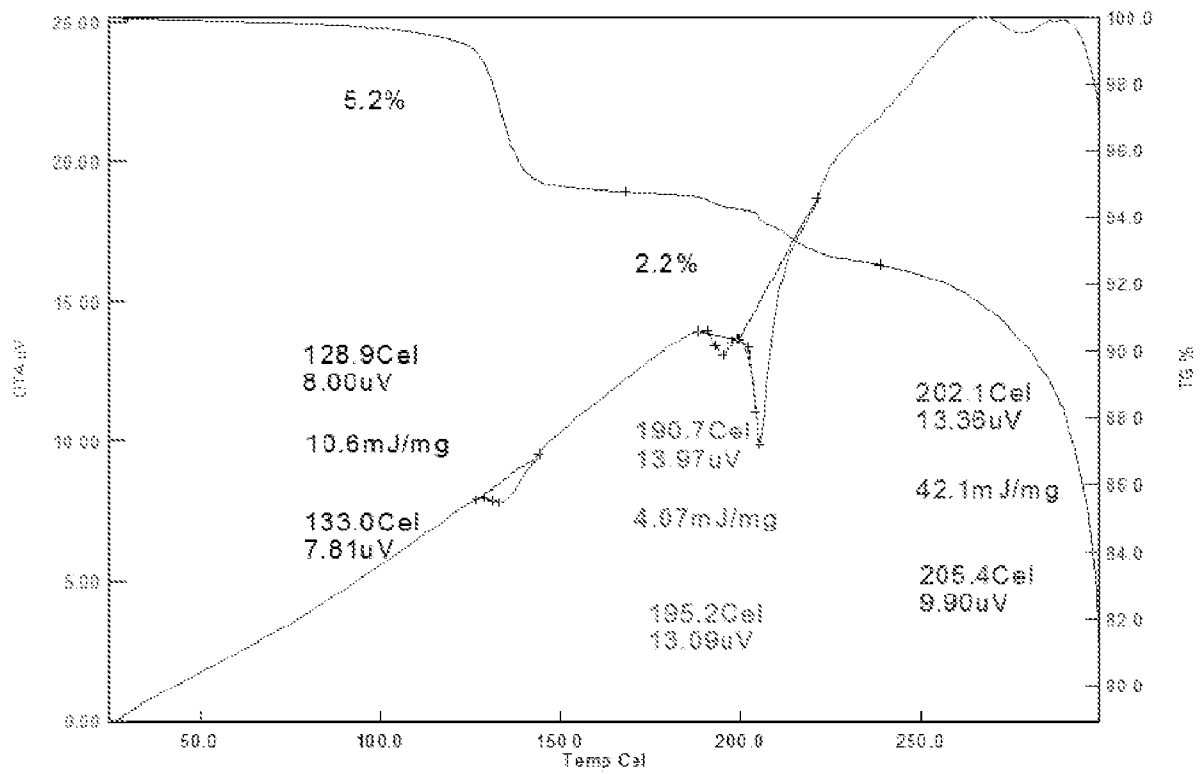


Fig. 56

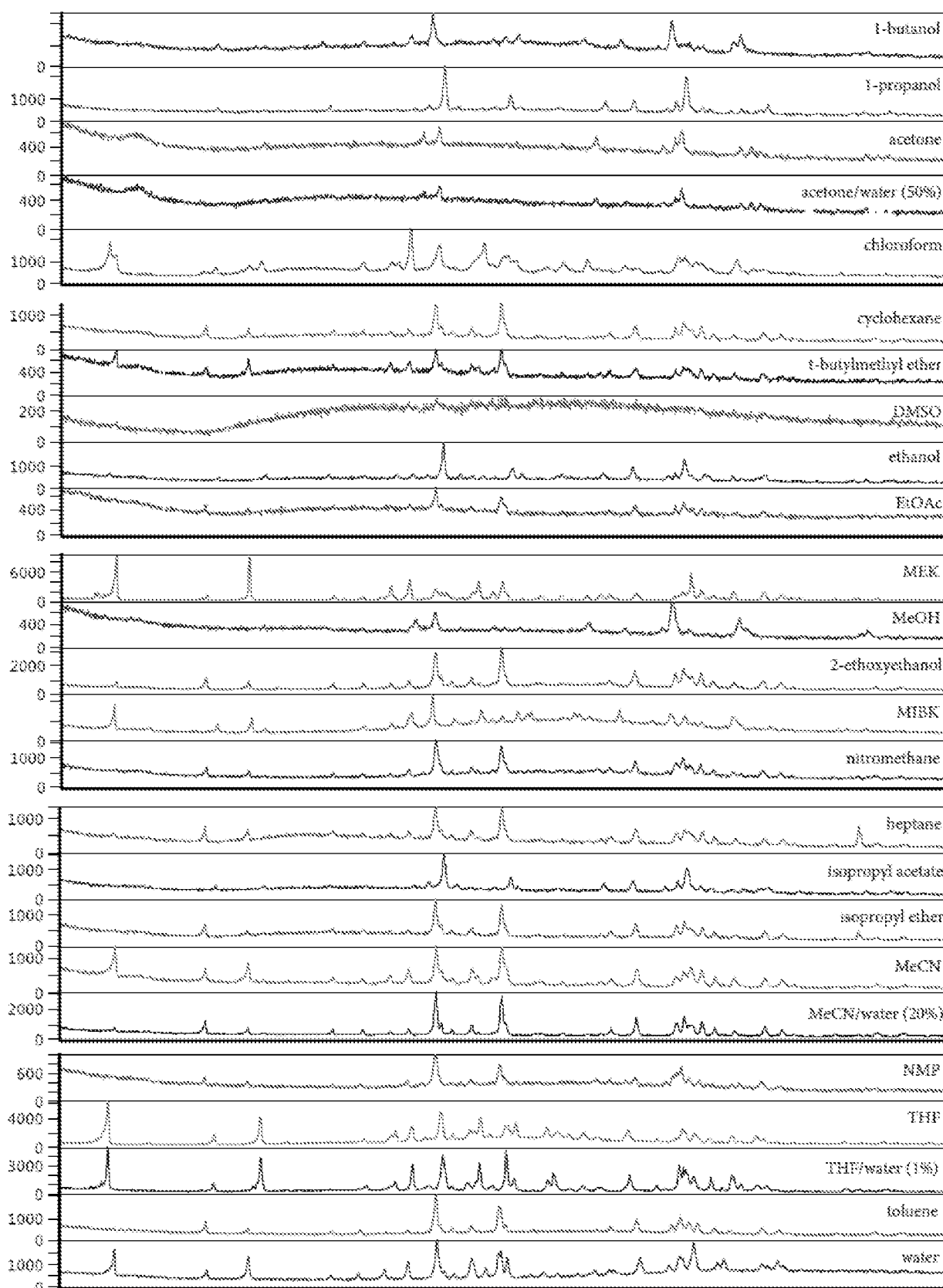


Fig. 57

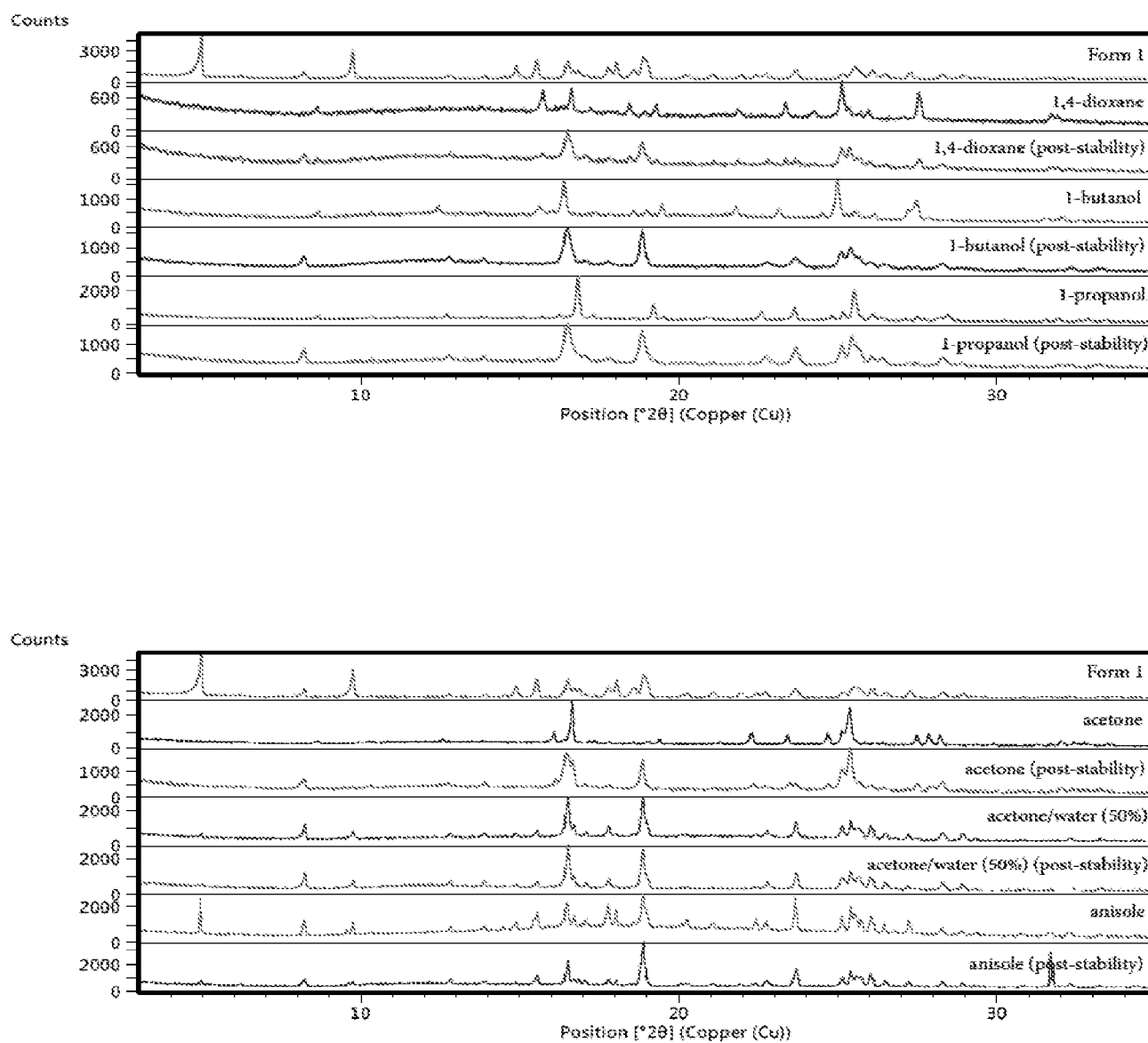


Fig. 58A

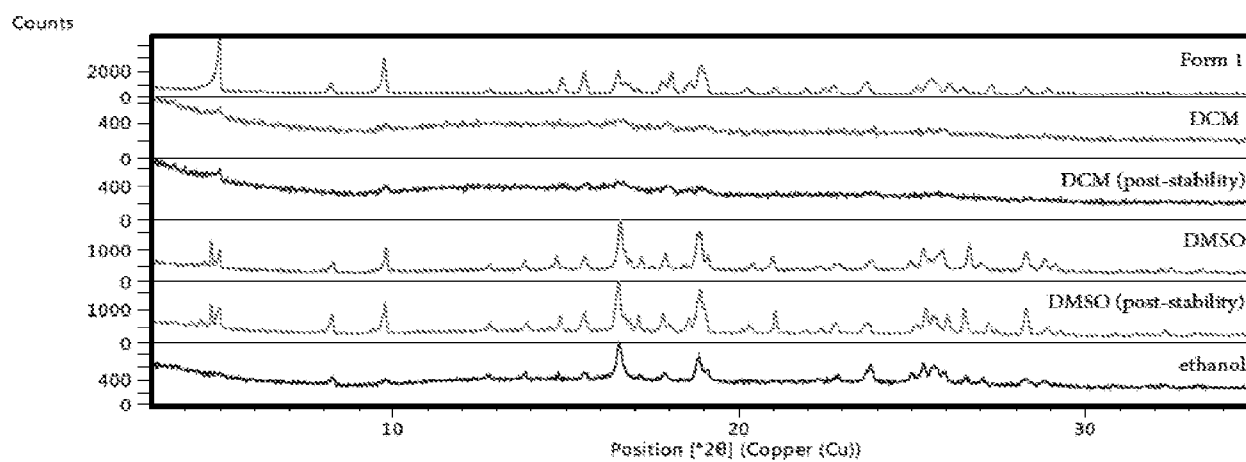
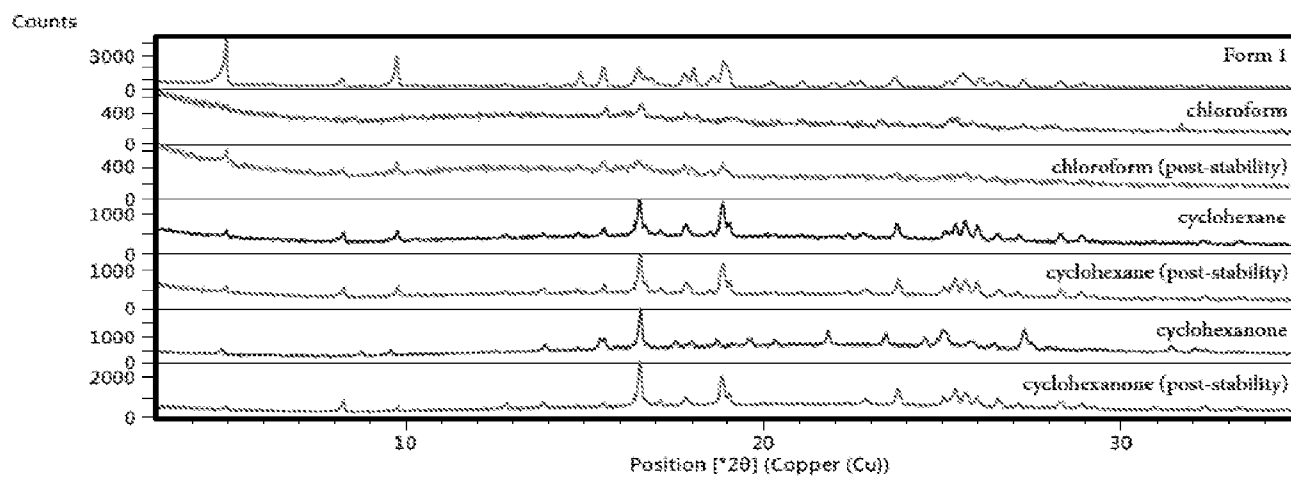


Fig. 58B

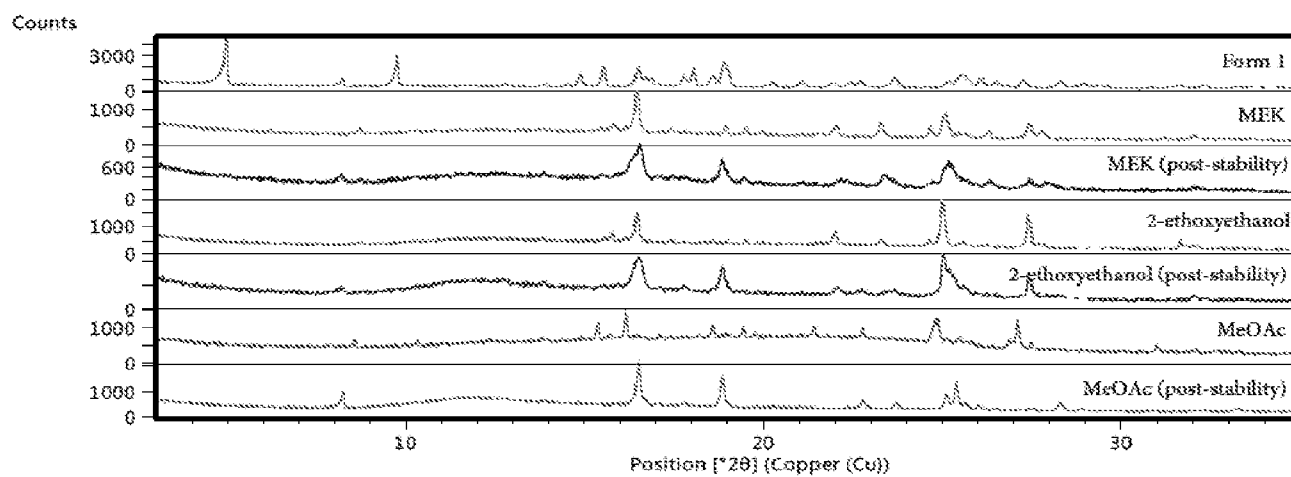
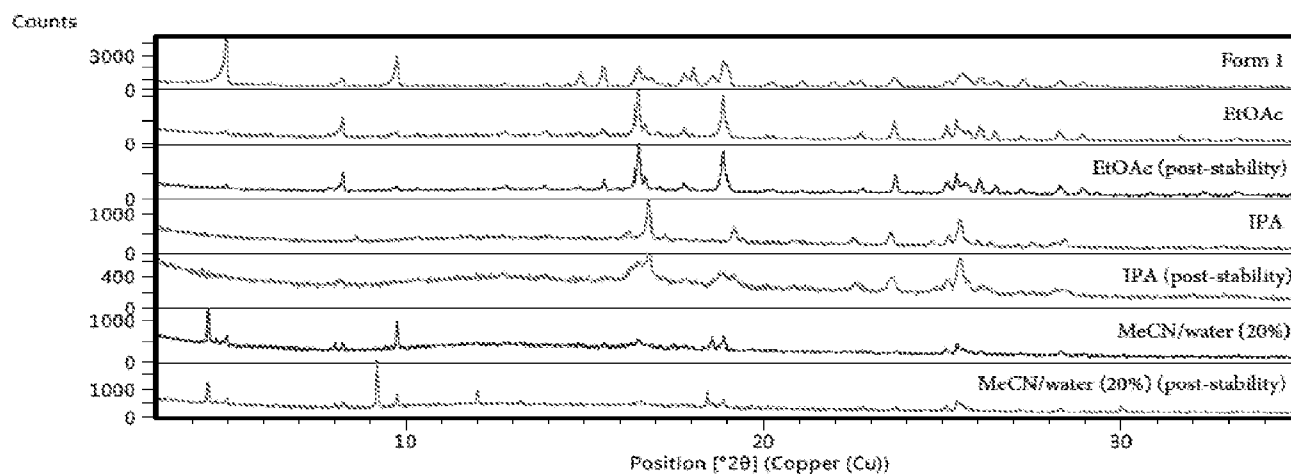


Fig. 58C

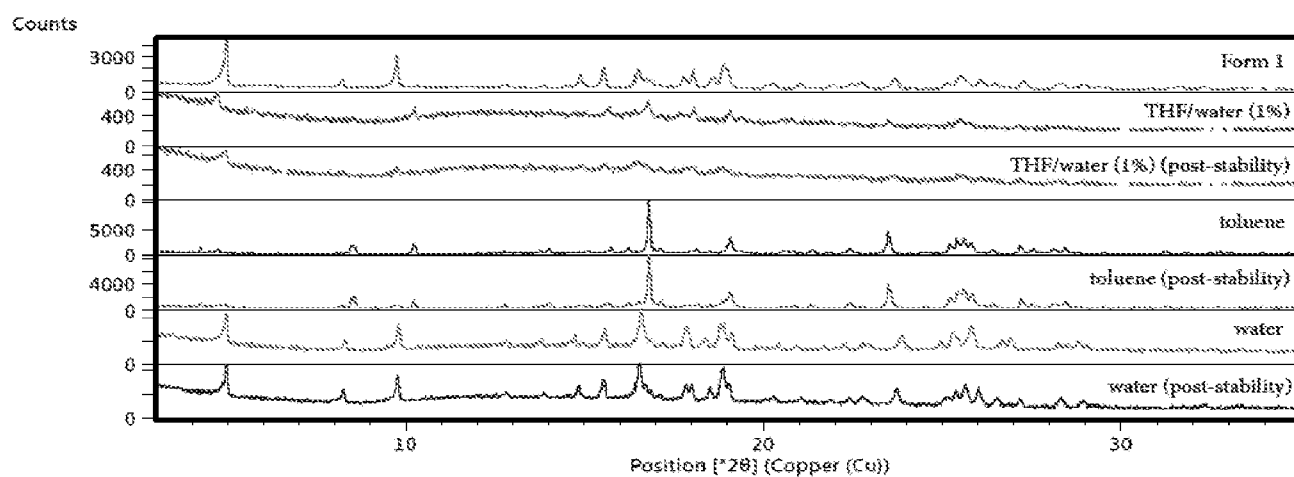
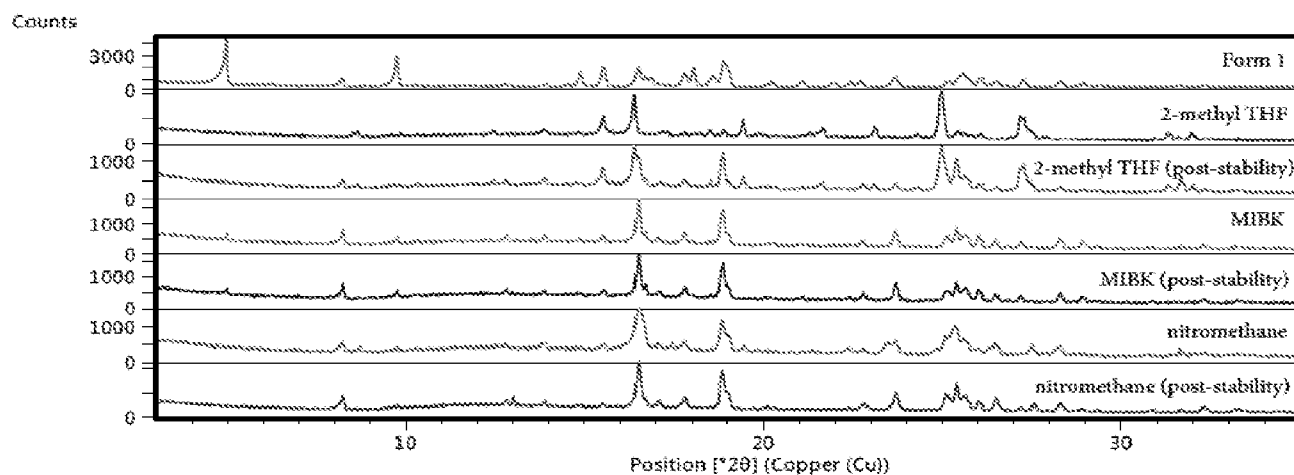


Fig. 58D

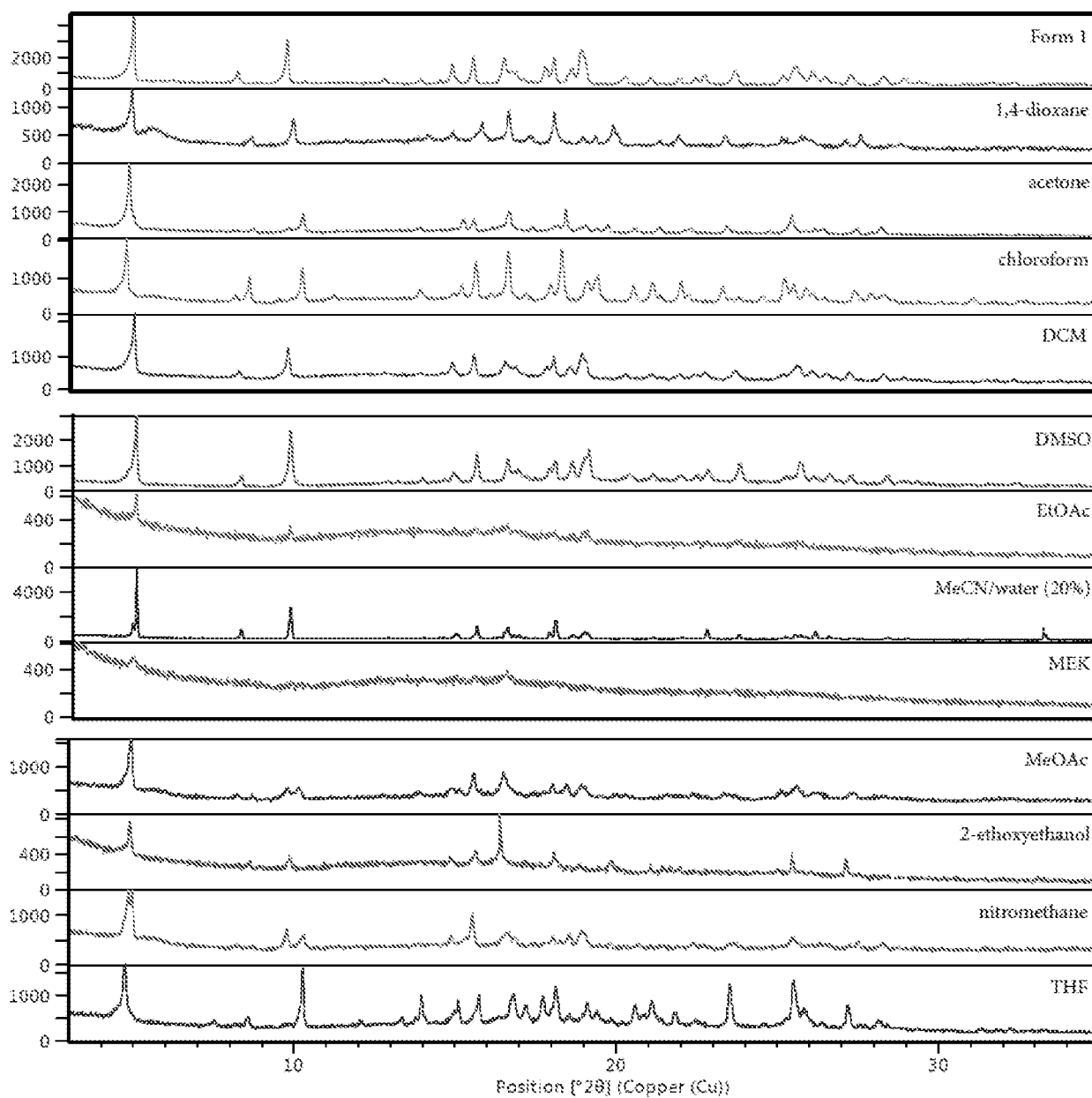


Fig. 59

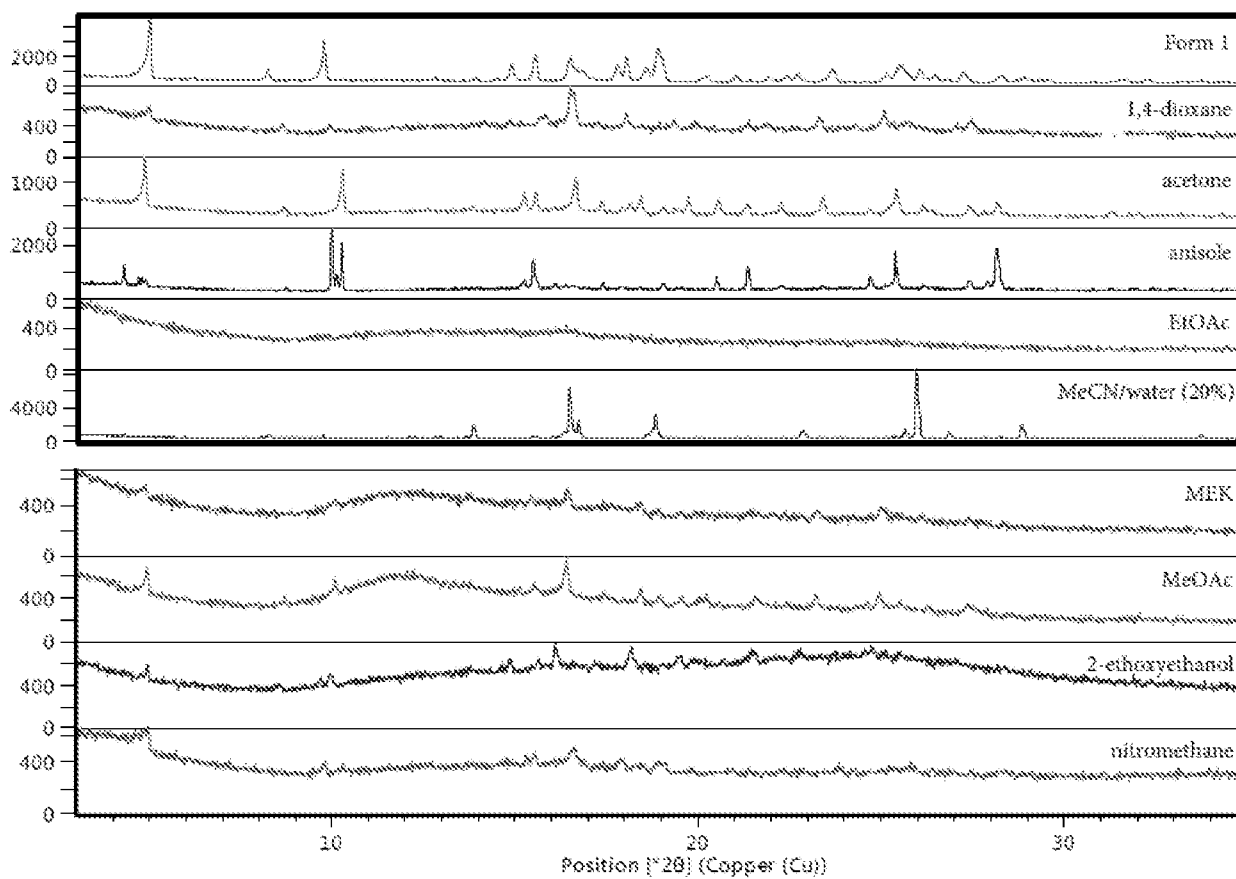


Fig. 60

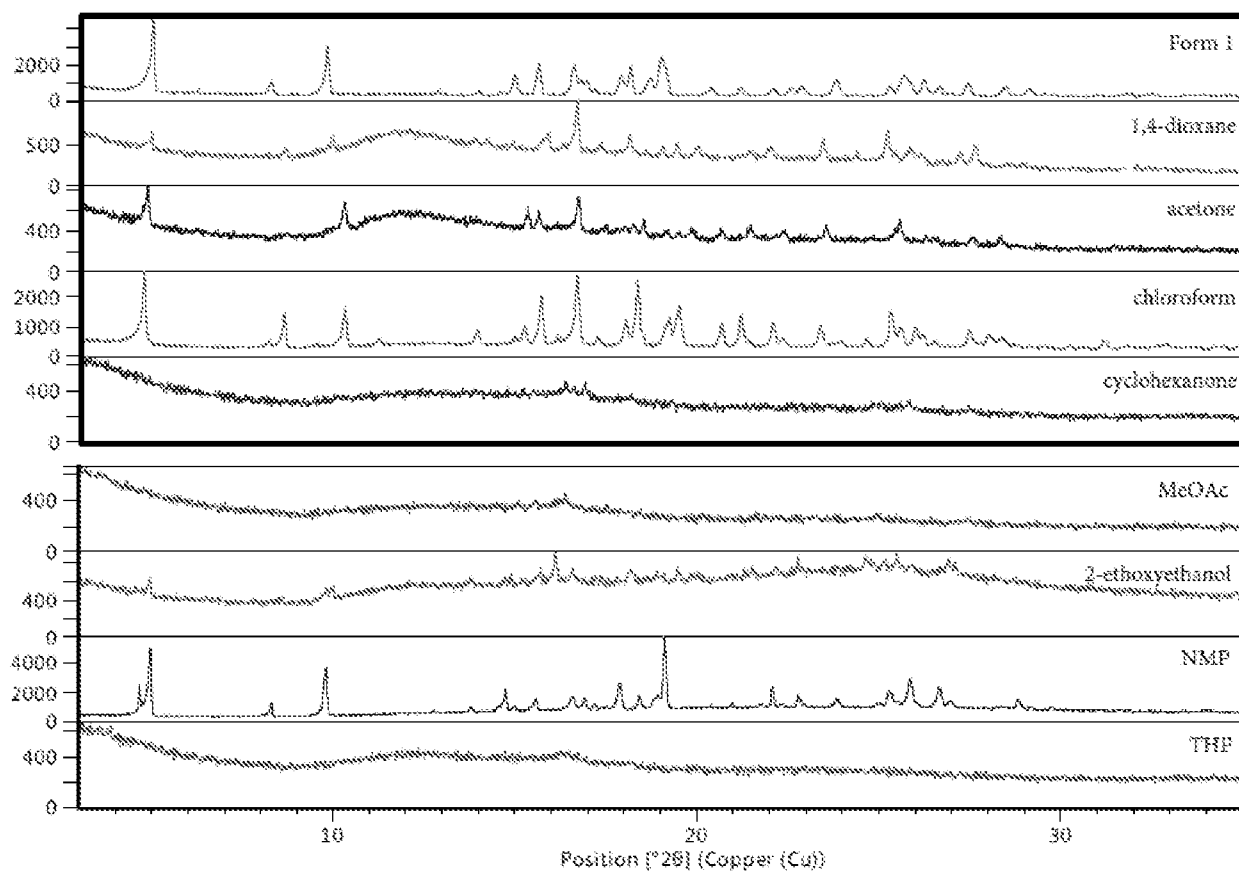


Fig. 61

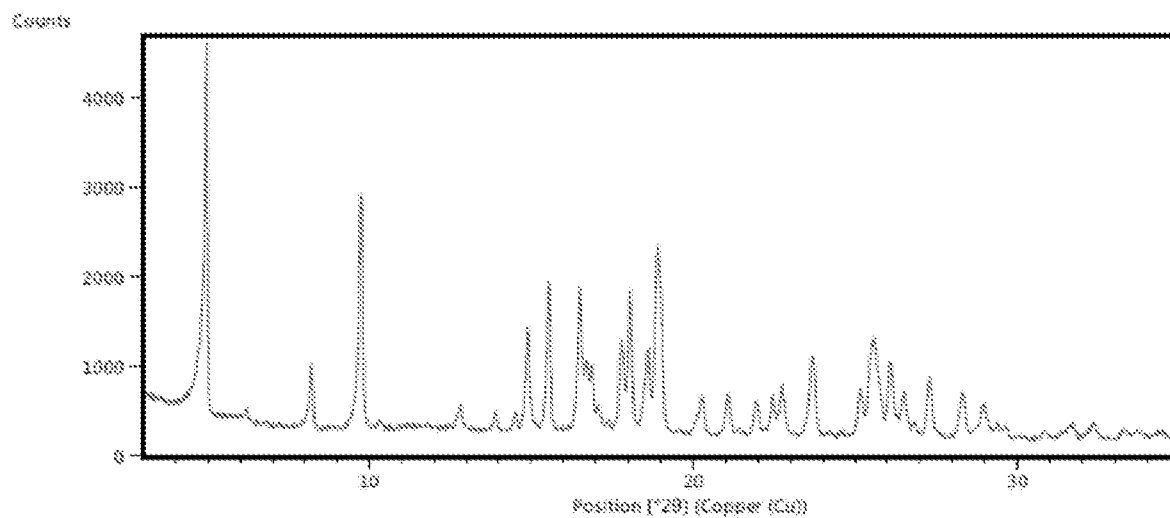


Fig. 62A

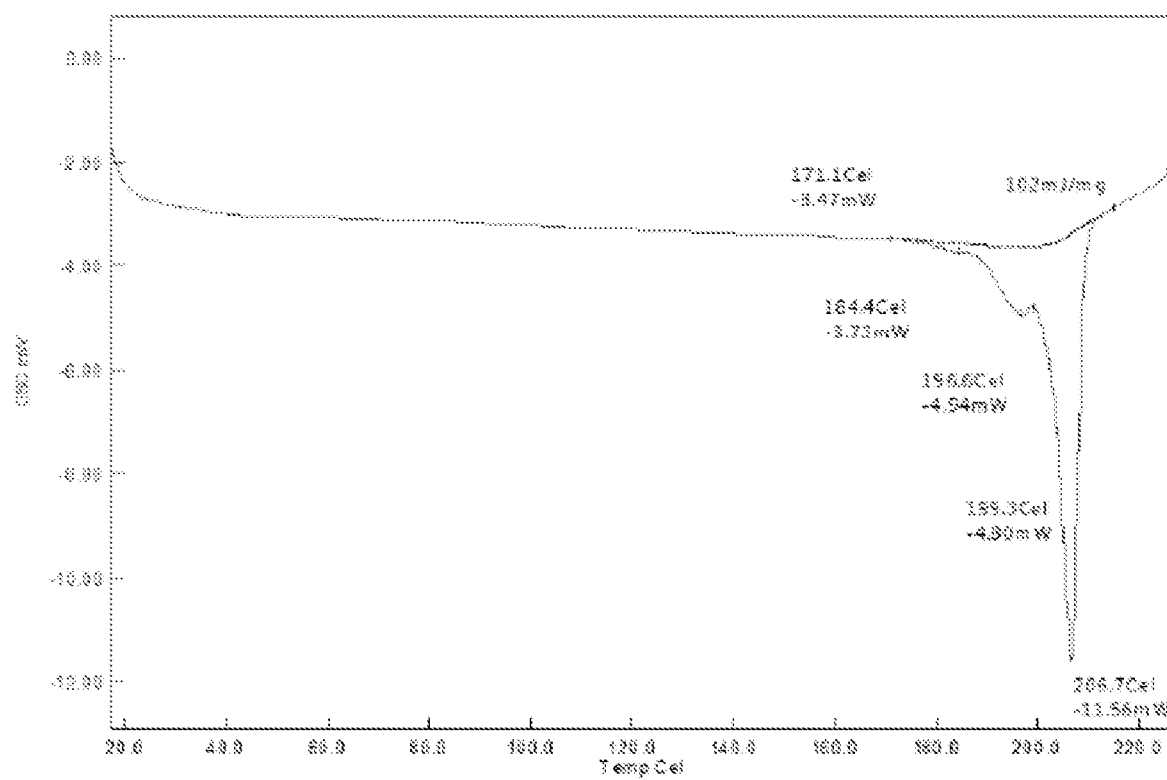


Fig. 62B

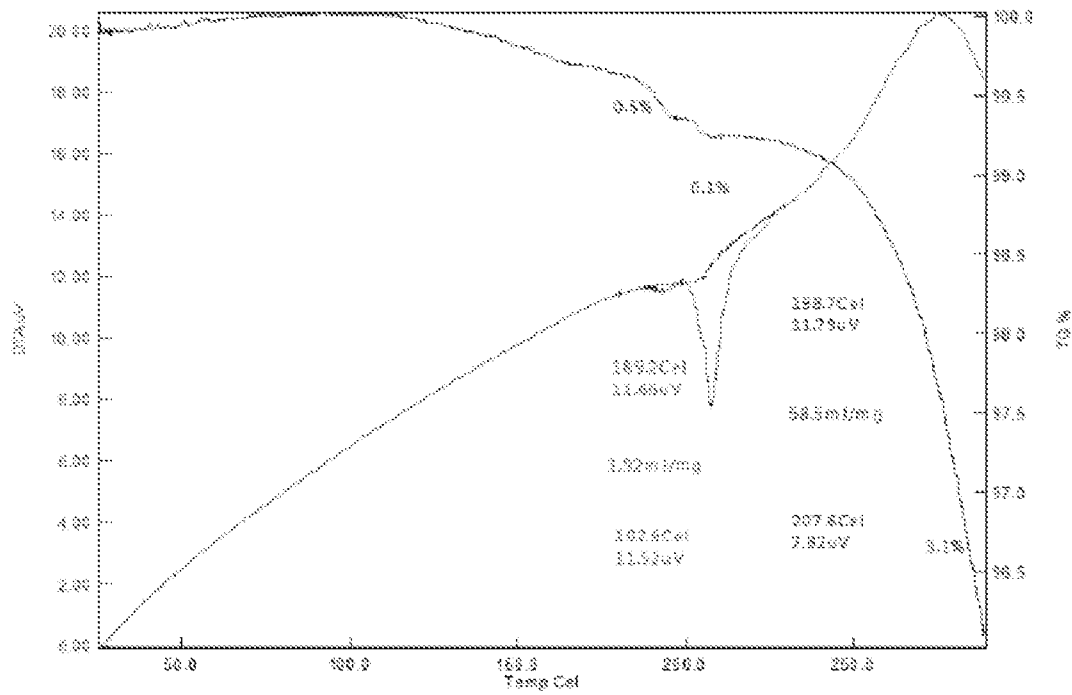


Fig. 62C

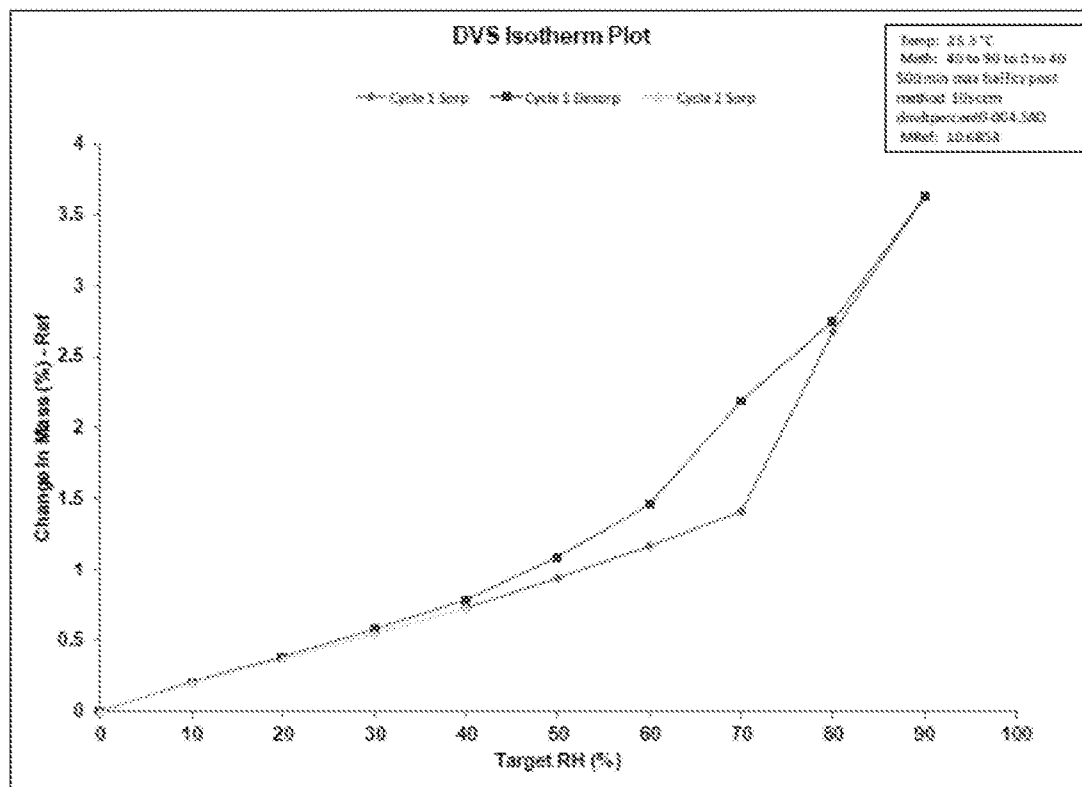


Fig. 62D

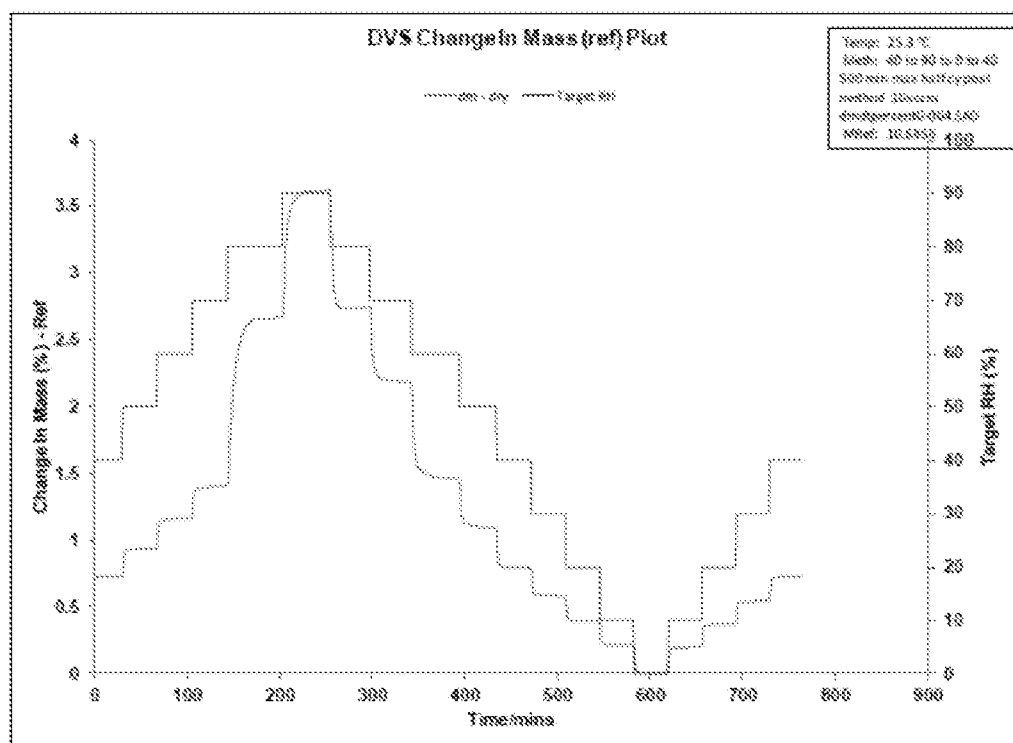


Fig. 62E

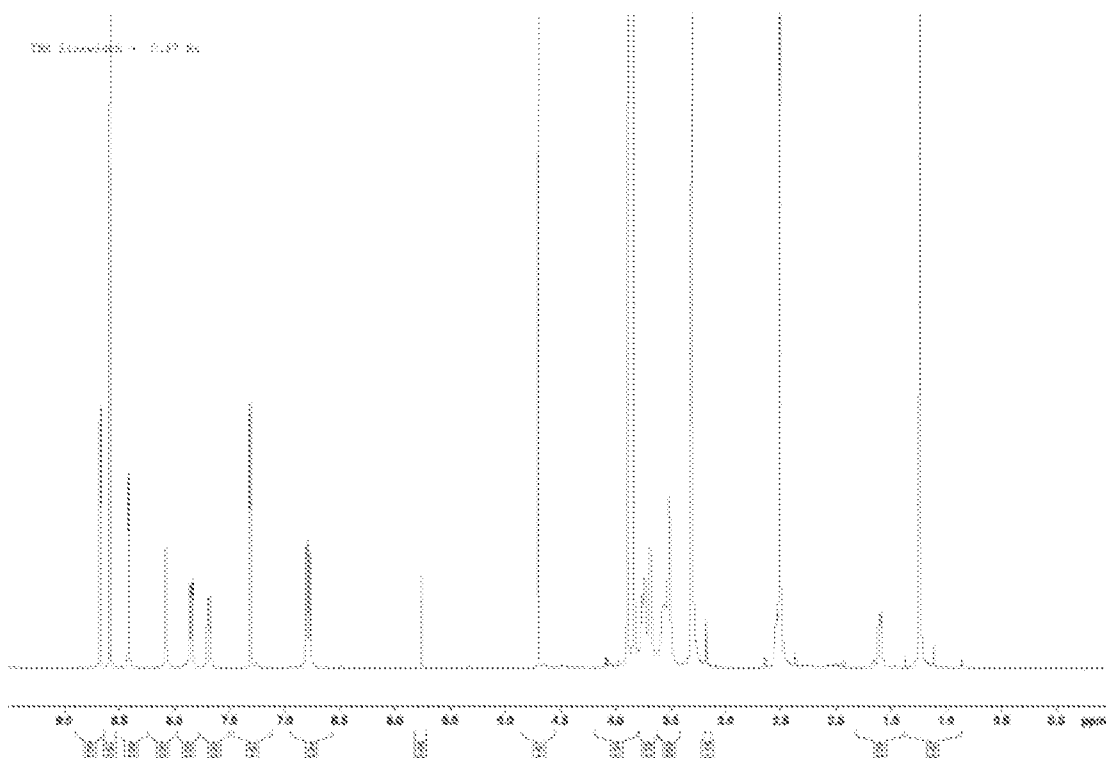


Fig. 62F

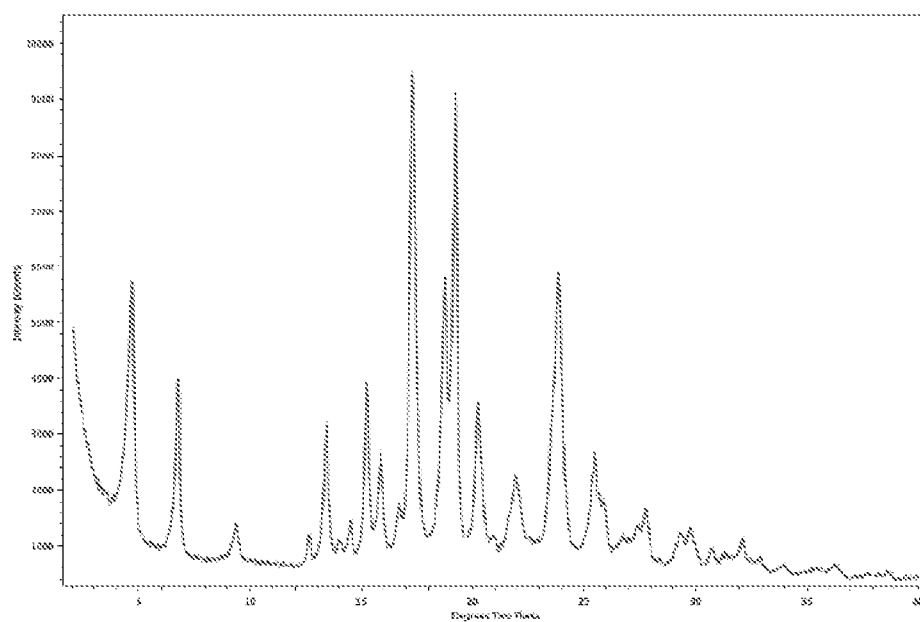


Fig. 63A

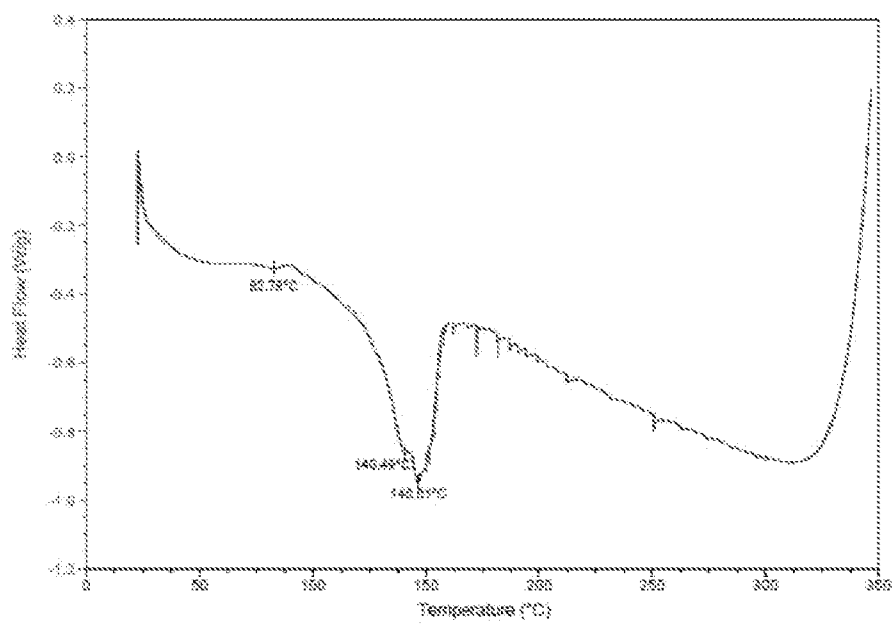


Fig. 63B

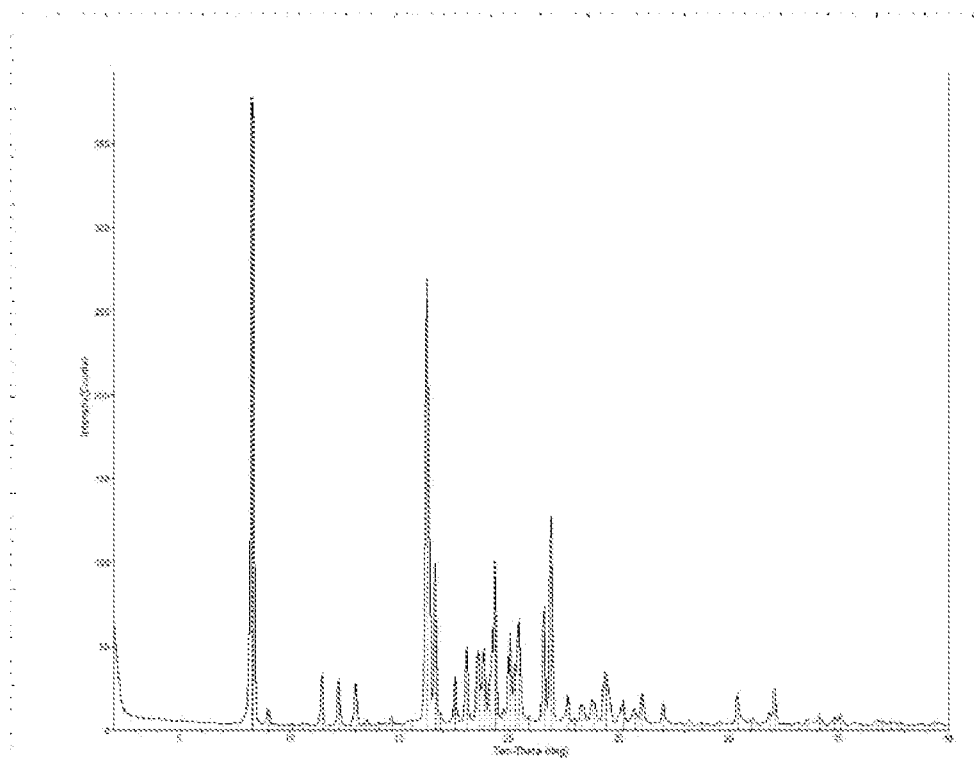


Fig. 64A

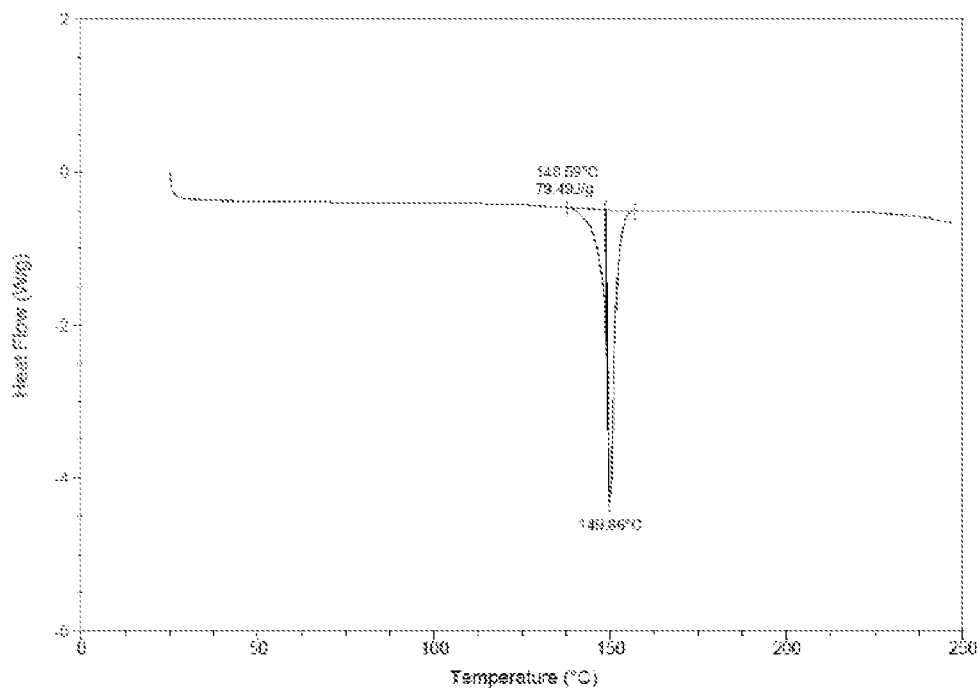


Fig. 64B

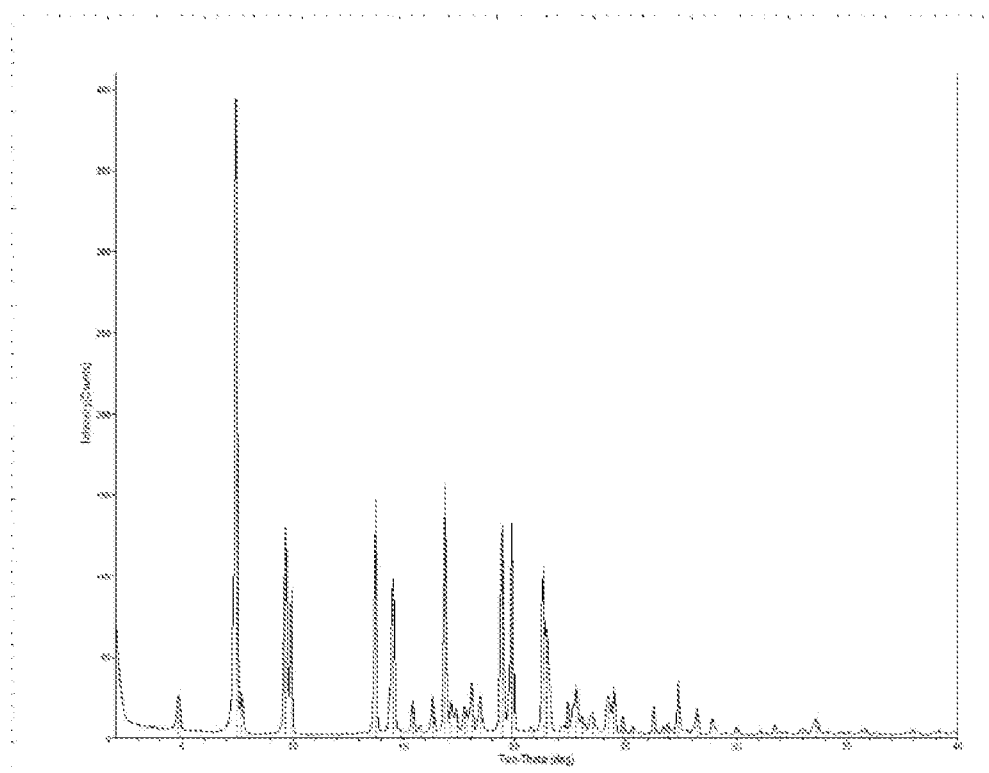


Fig. 65A

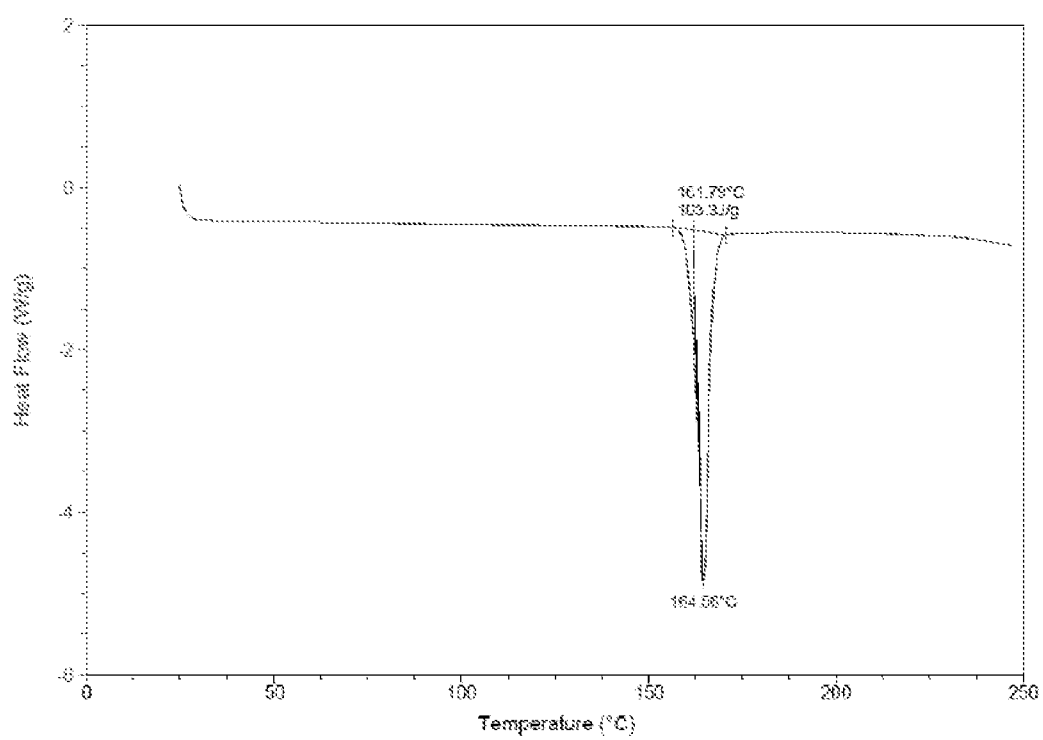


Fig. 65B

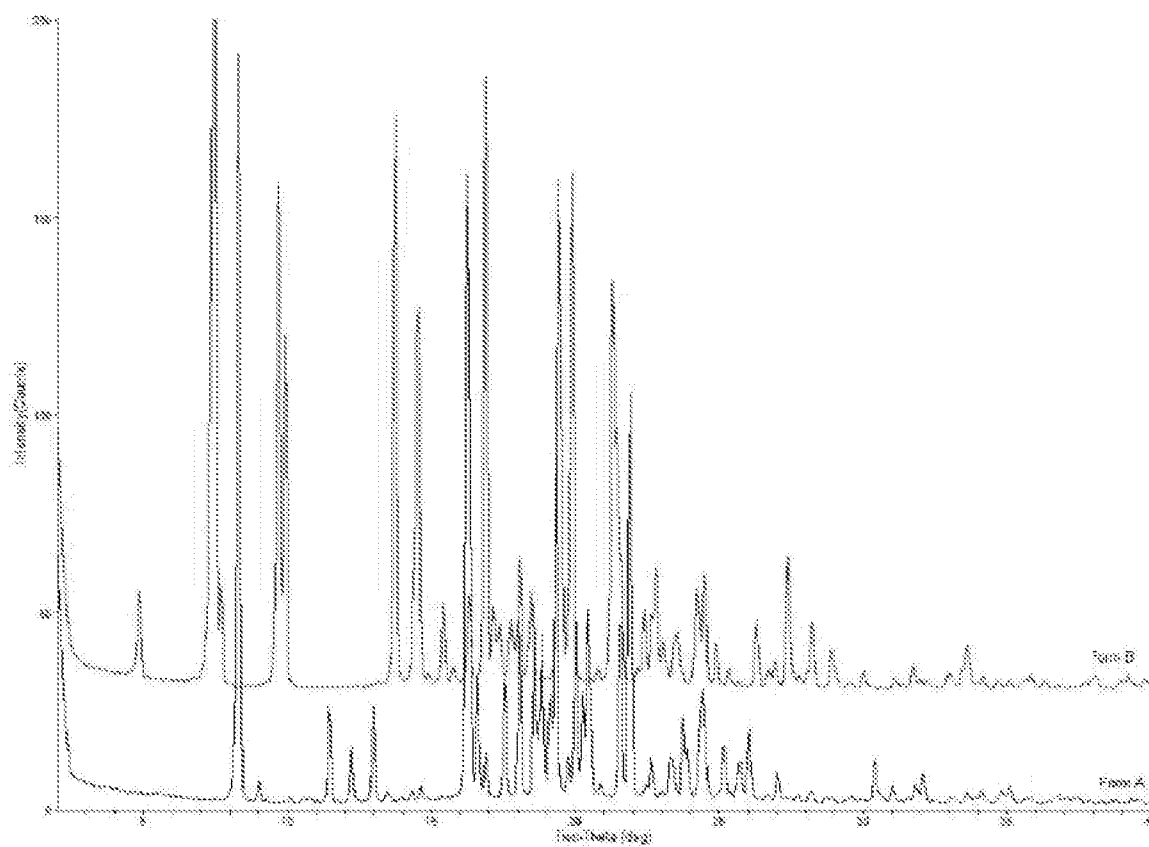
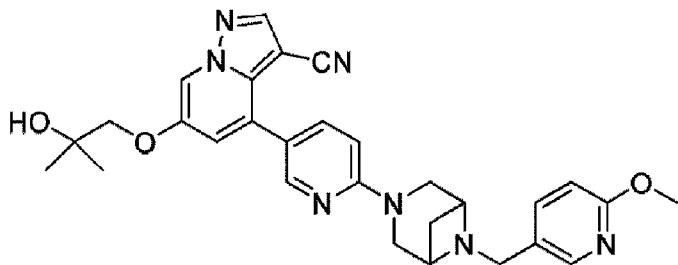


Fig. 66



(II)